

SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND
ANTIOBESITY AGENTS AND METHOD

ind. A
A This is a continuation-in-part of U.S. application
Serial No. 09/664,598, filed September 18, 2000^{now abandoned} which
application takes priority from U.S. provisional
application No. 60/155,400 filed September 22, 1999.

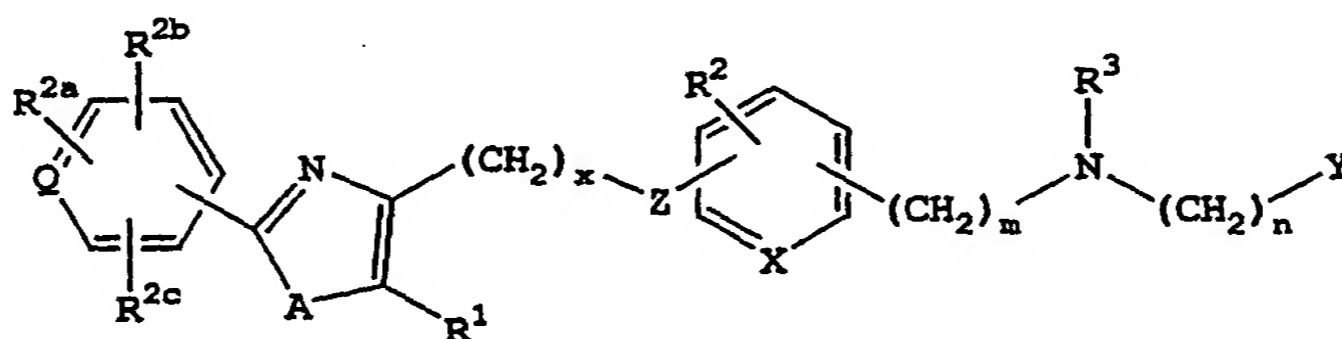
Field of the Invention

10 The present invention relates to novel substituted
acid derivatives which modulate blood glucose levels,
triglyceride levels, insulin levels and non-esterified
fatty acid (NEFA) levels, and thus are particularly
useful in the treatment of diabetes and obesity, and to a
15 method for treating diabetes, especially Type 2 diabetes,
as well as hyperglycemia, hyperinsulinemia,
hyperlipidemia, obesity, atherosclerosis and related
diseases employing such substituted acid derivatives
alone or in combination with another antidiabetic agent
20 and/or a hypolipidemic agent.

Description of the Invention

In accordance with the present invention,
substituted acid derivatives are provided which have the
25 structure I

I



wherein x is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R¹ is H or alkyl;

X is CH or N;



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5 aminocarbonylarylalkyl;

10 structure $P(O)(OR^{4a})_2$, (where R^{4a} is H or a prodrug ester);

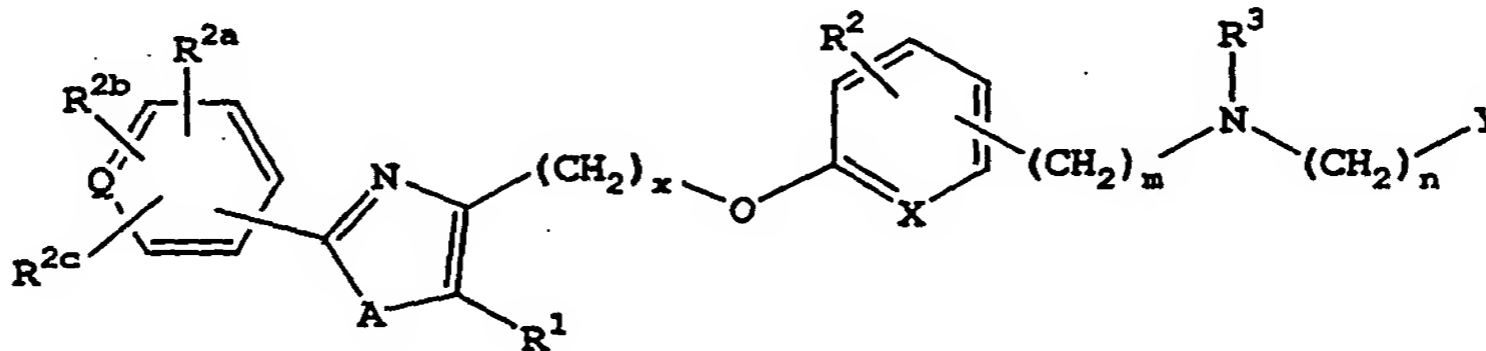
$(CH_2)_x$, $(CH_2)_n$ and $(CH_2)_m$ may be optionally substituted with 1, 2 or 3 substituents;

15 thereof, with the proviso that

where X is CH, A is O, Q is C, Z is O, and Y is CO_2R^4 , then R^3 is other than H or alkyl containing 1 to 5 carbons in the normal chain.

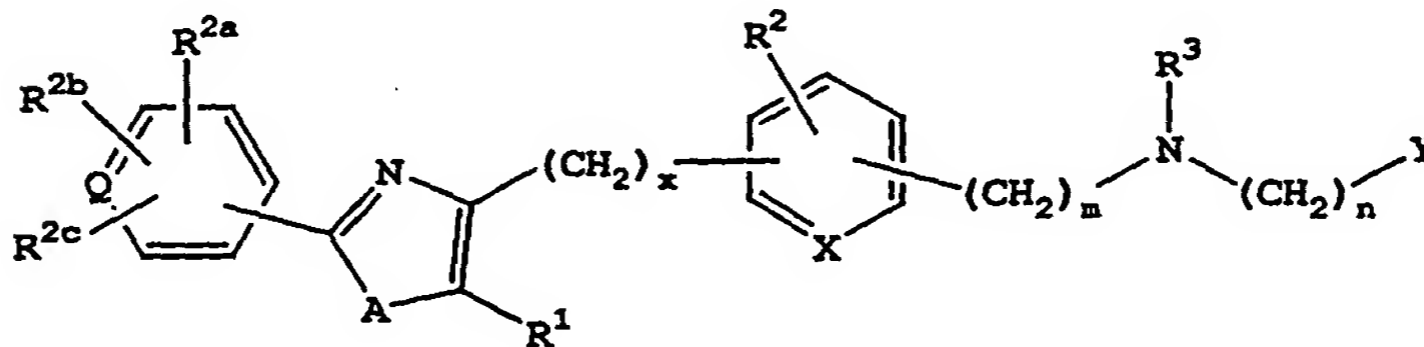
20 have the structure

Ia



or

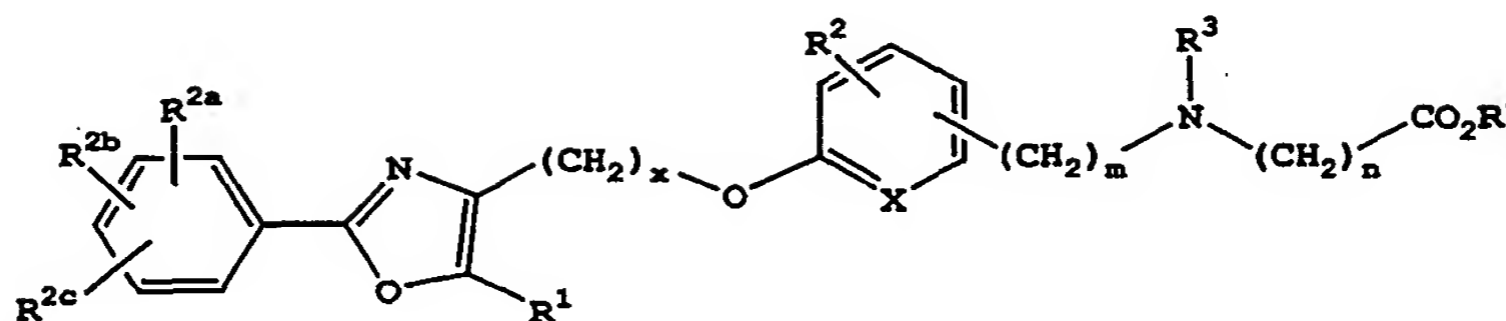
Ib



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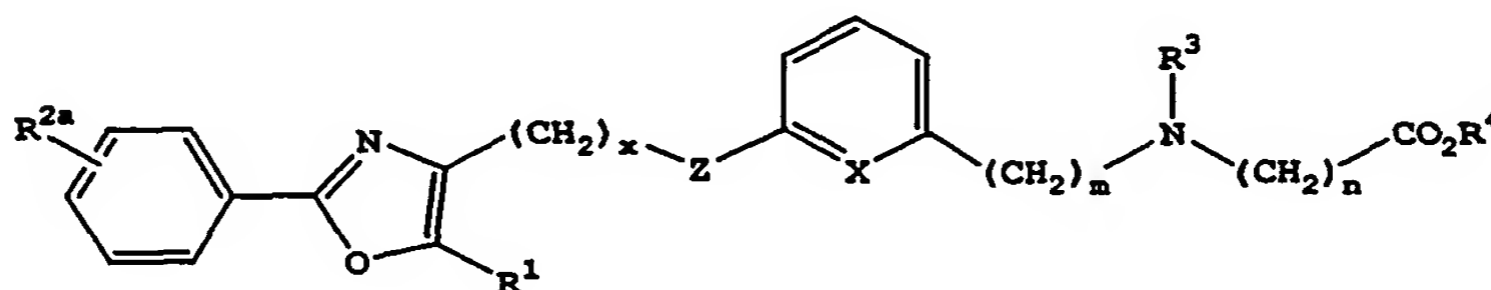
Preferred are compounds of formula I of the invention having the structure

IA



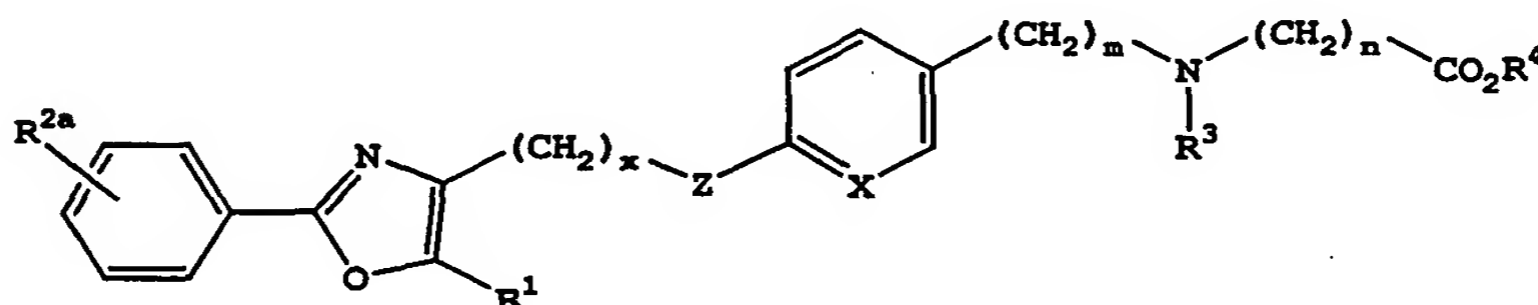
More preferred are compounds of formula I of the invention having the structures

5 IB



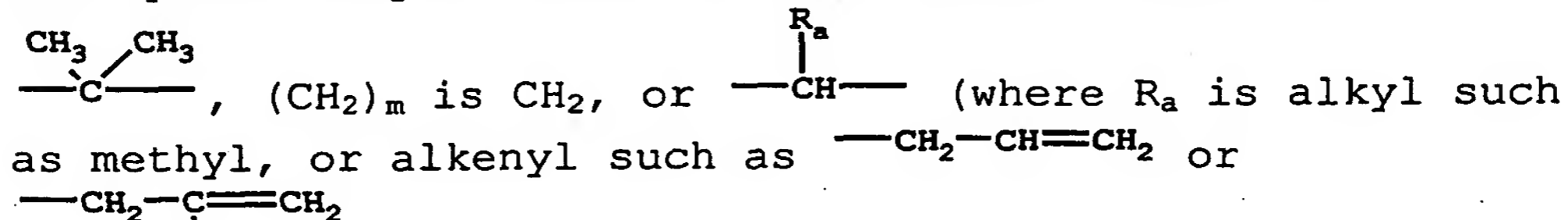
or

IC



10

In the above compounds, it is most preferred that R^{2a} is alkoxy, but more preferably H, Z is a bond, but more preferably O, $(CH_2)_x$ is CH_2 , $(CH_2)_2$, $(CH_2)_3$, or

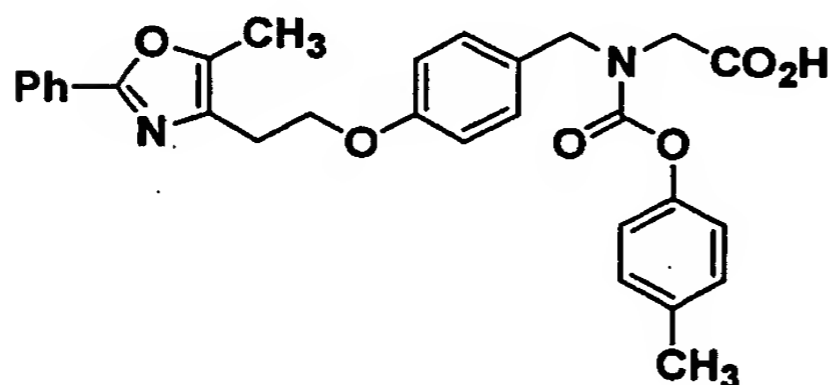
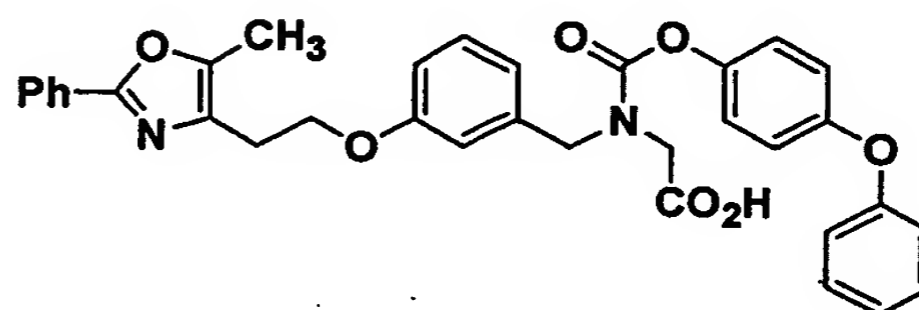
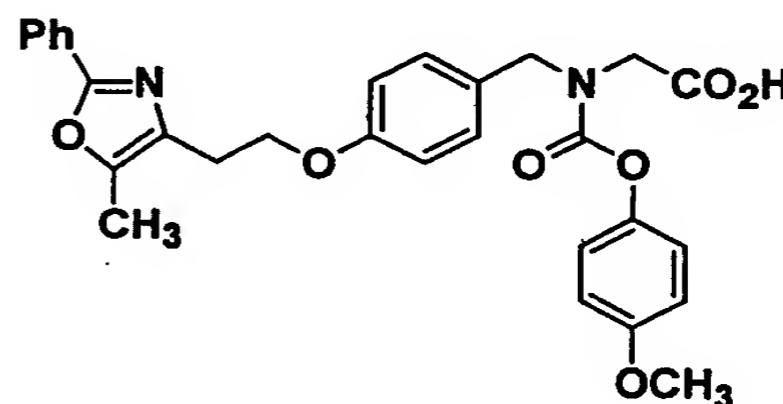
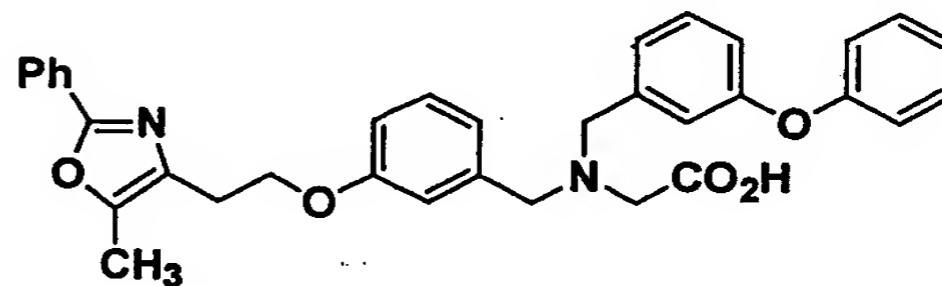
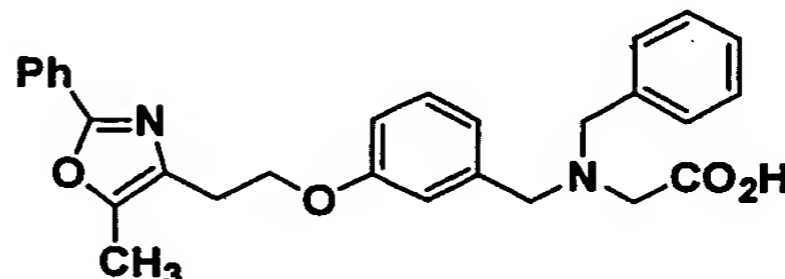
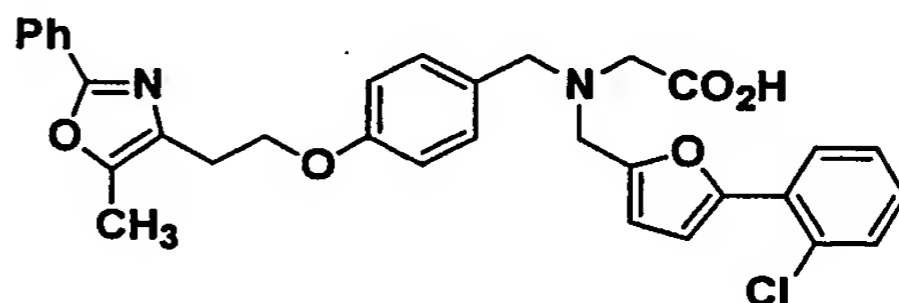


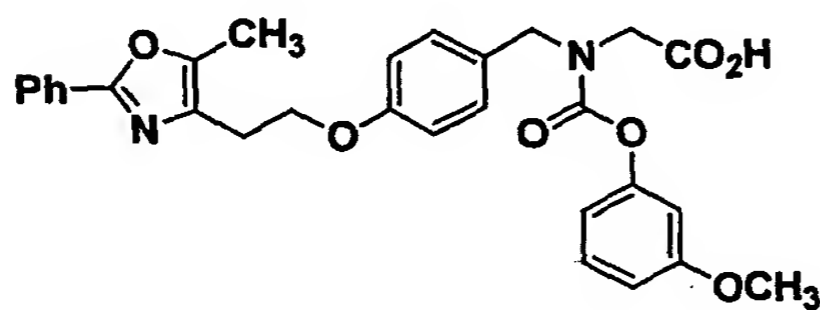
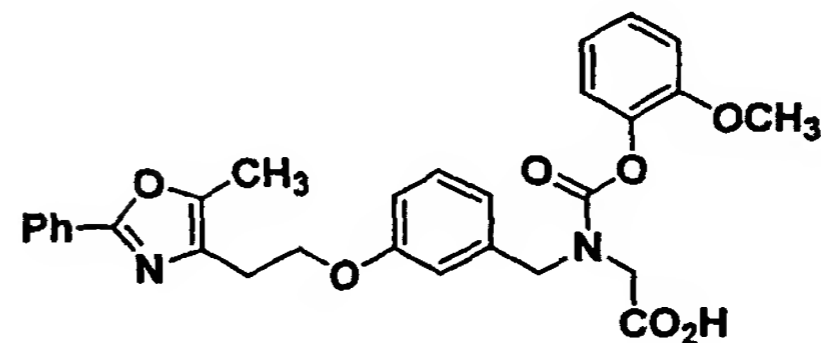
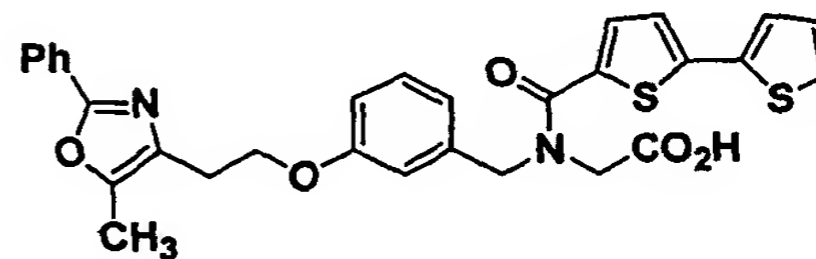
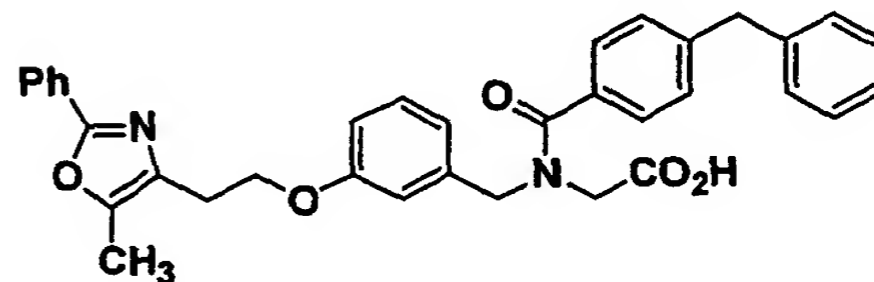
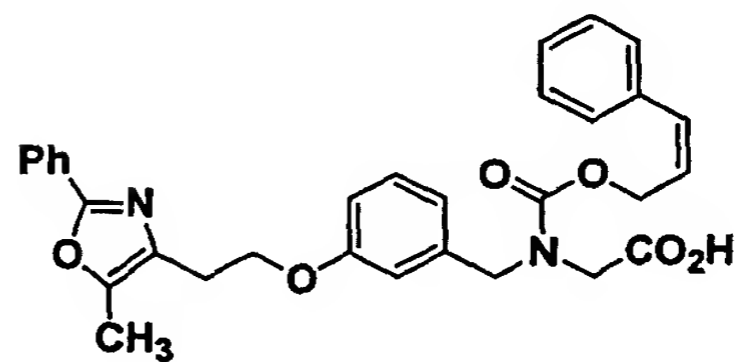
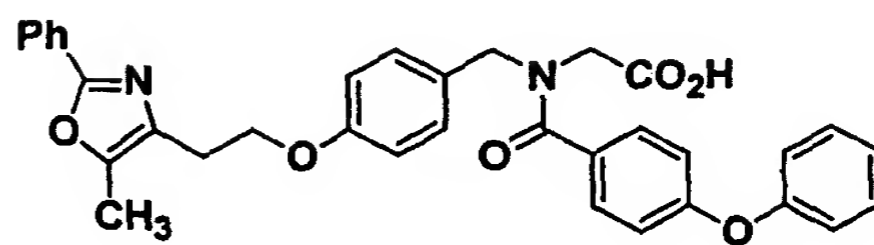
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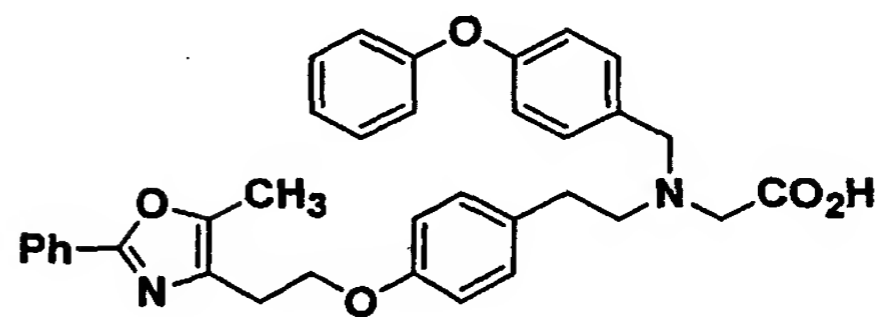
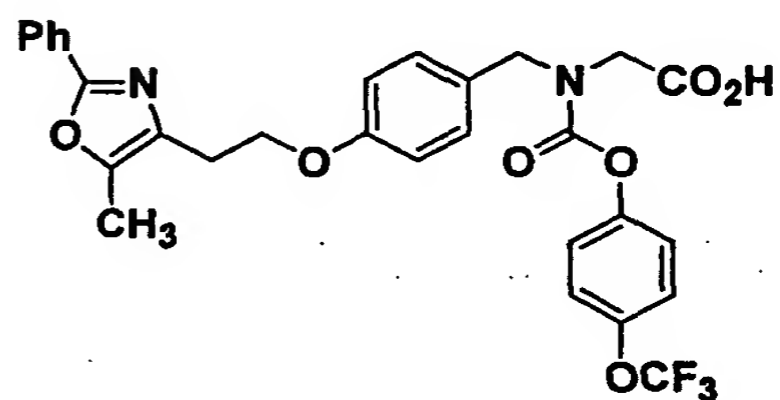
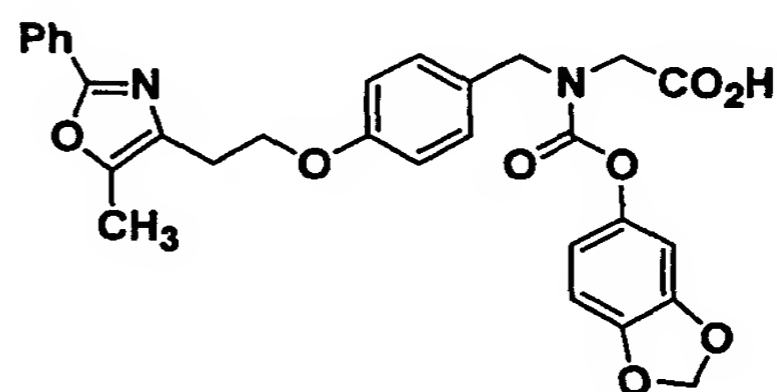
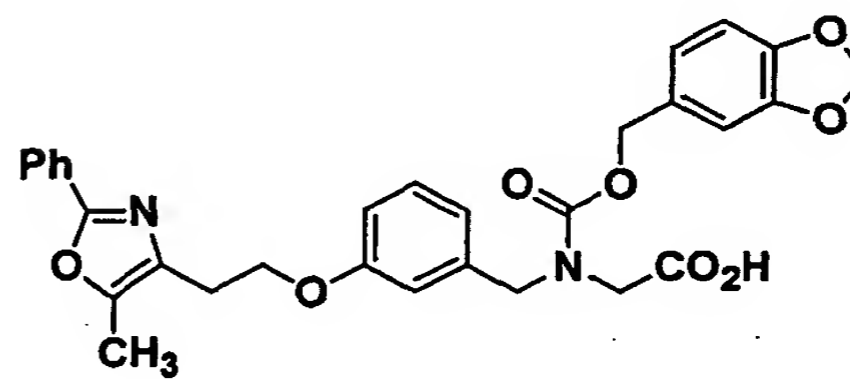
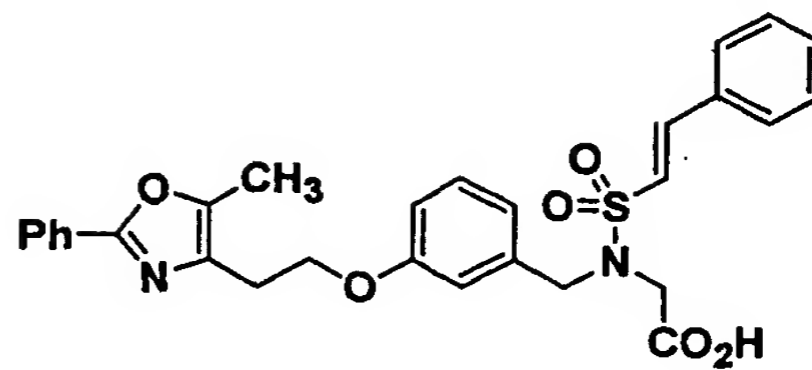
), $(CH_2)_n$ is CH_2 , R^1 is lower alkyl, preferably $-CH_3$, R^2 is H, R^{2a} is H, R^4 is H, X is CH, and R^3 is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl, haloaryloxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl, cycloalkyloxyaryloxycarbonyl, heteroaryl-

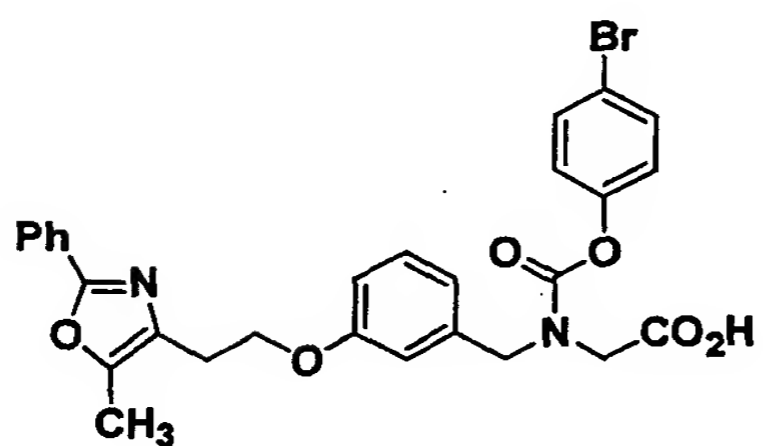
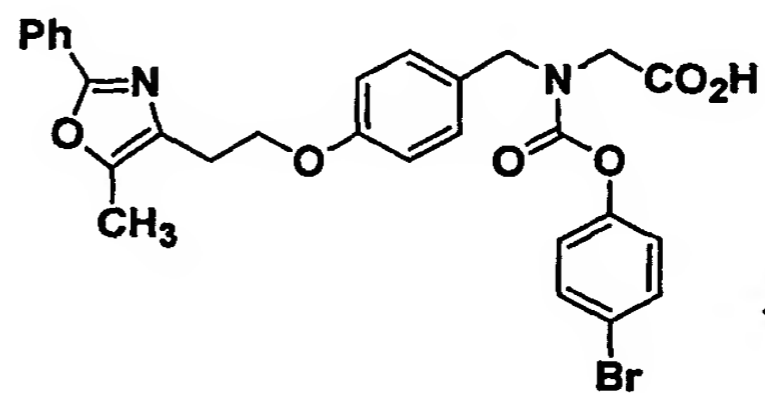
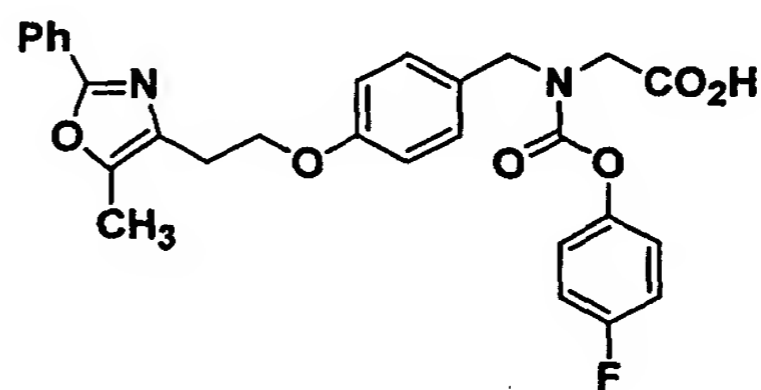
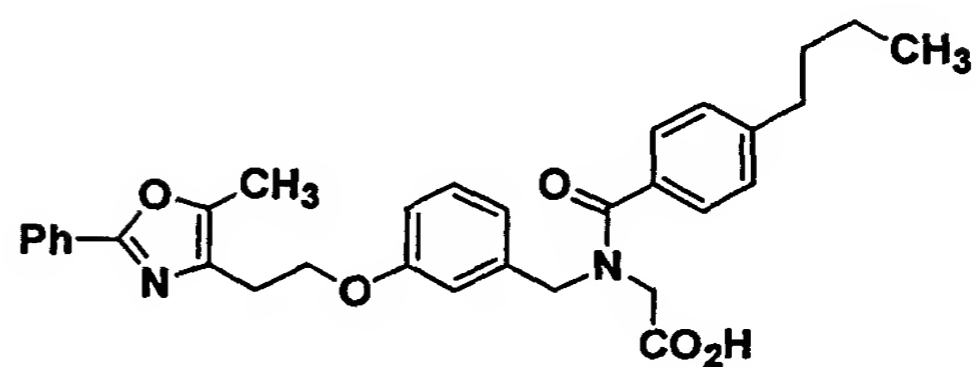
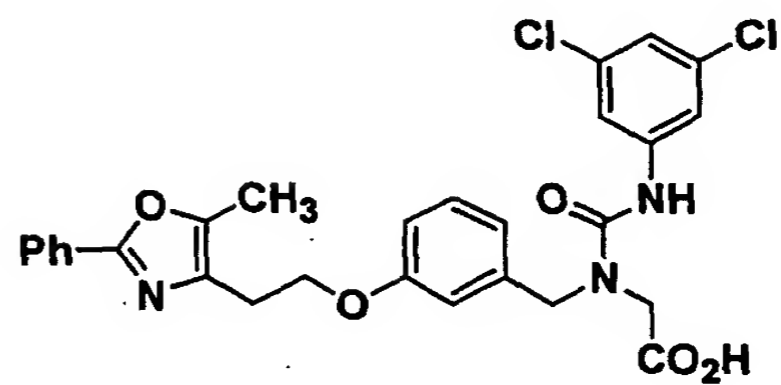
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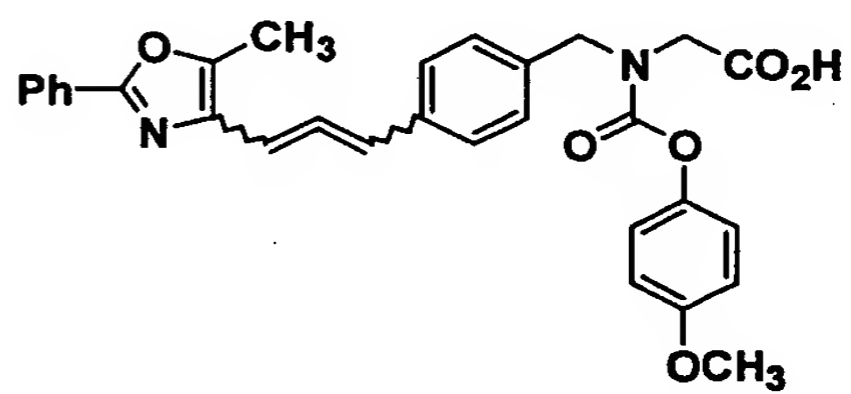
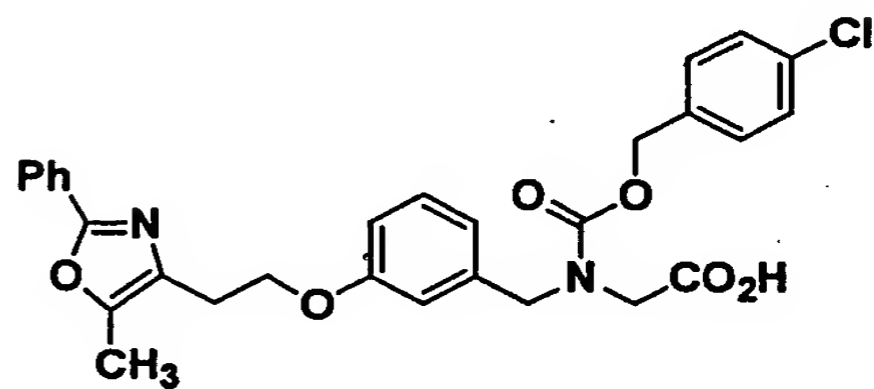
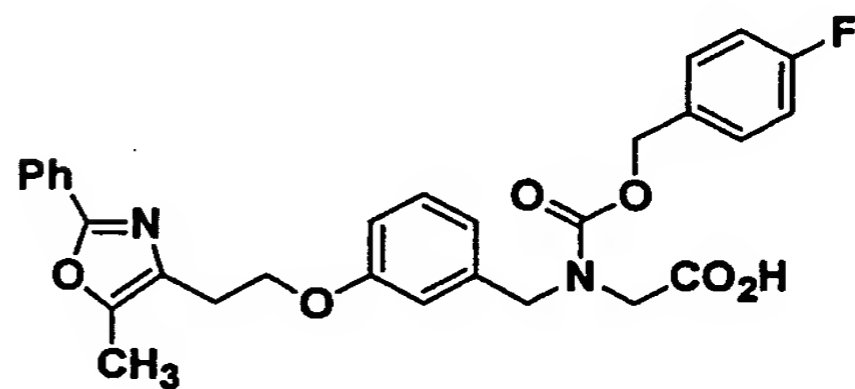
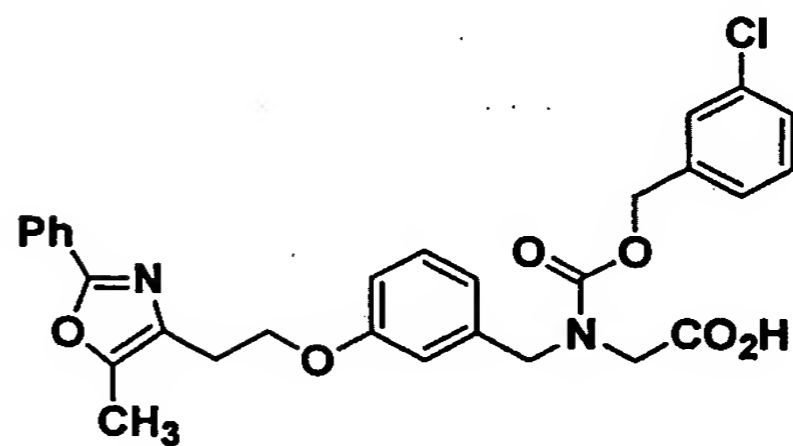
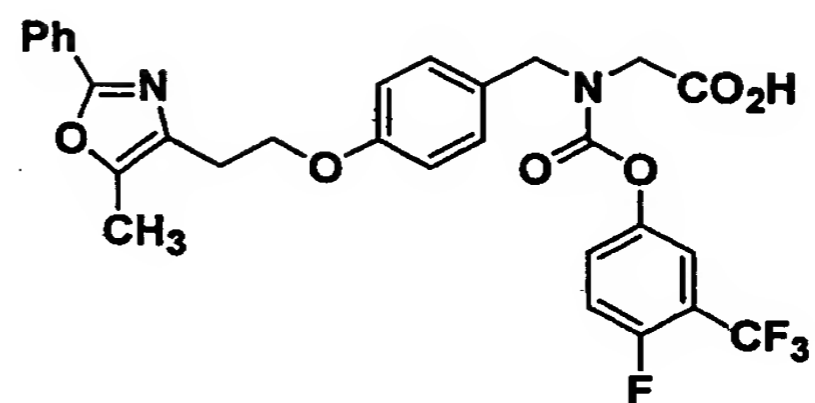
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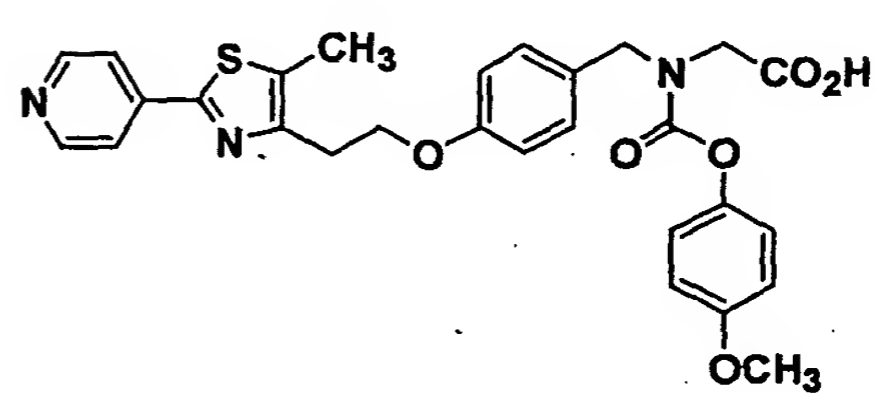
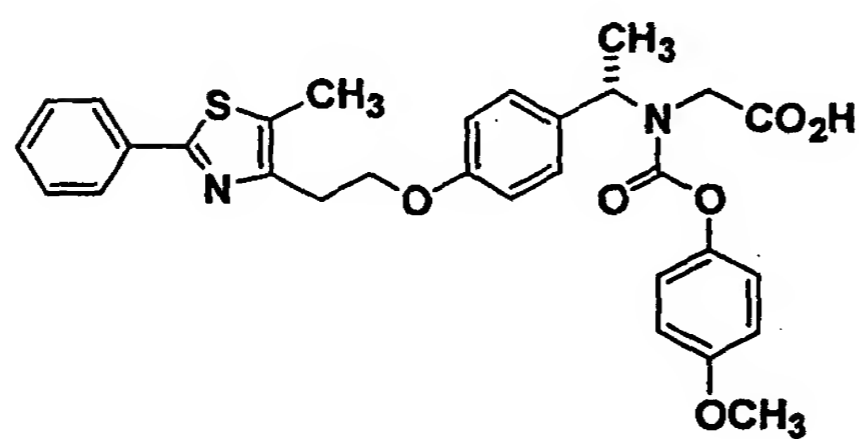
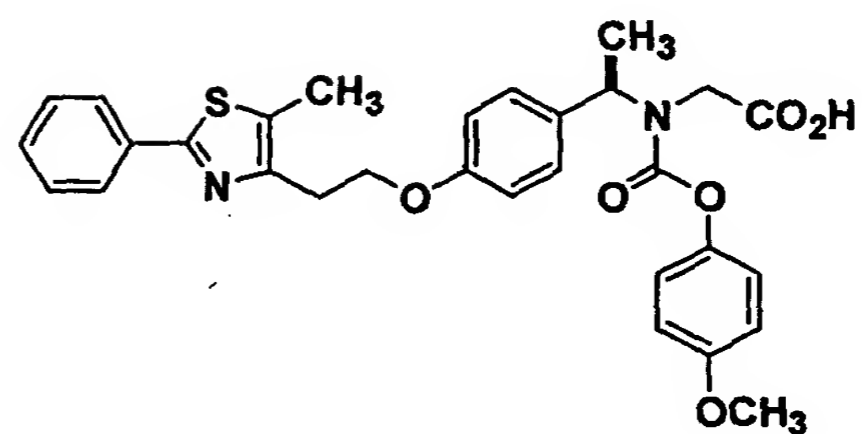
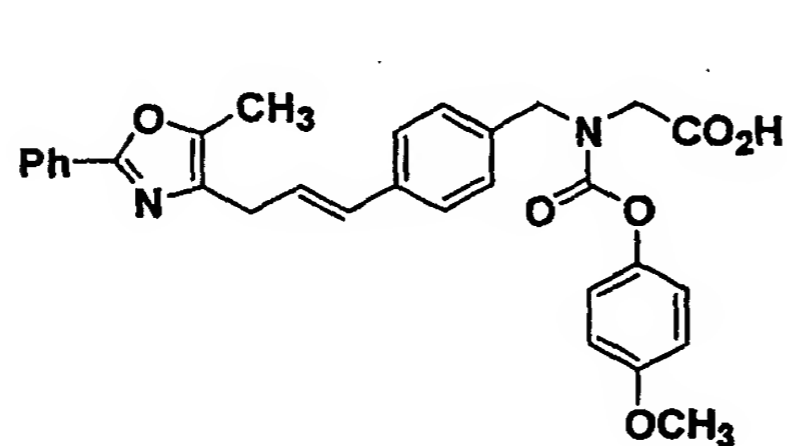
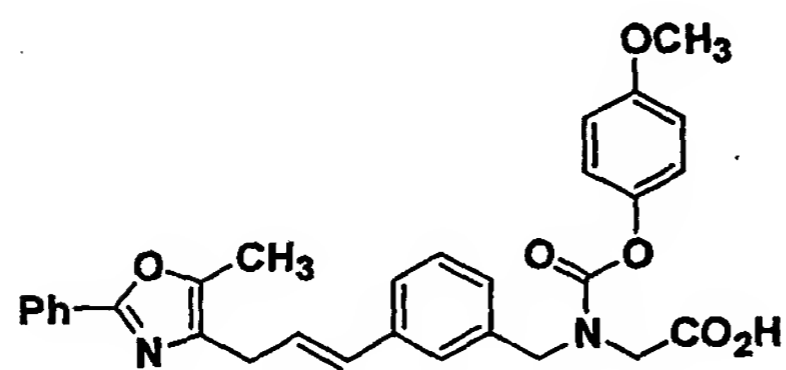
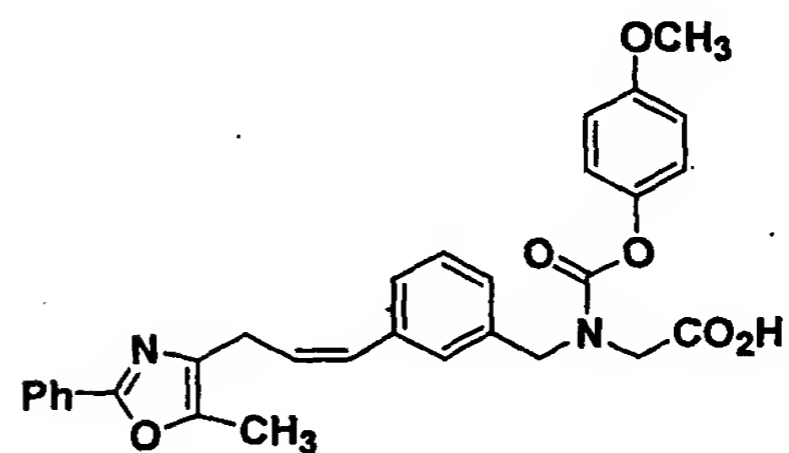
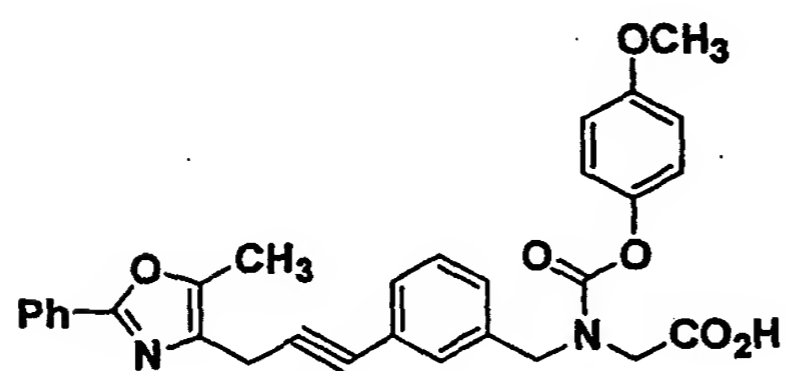
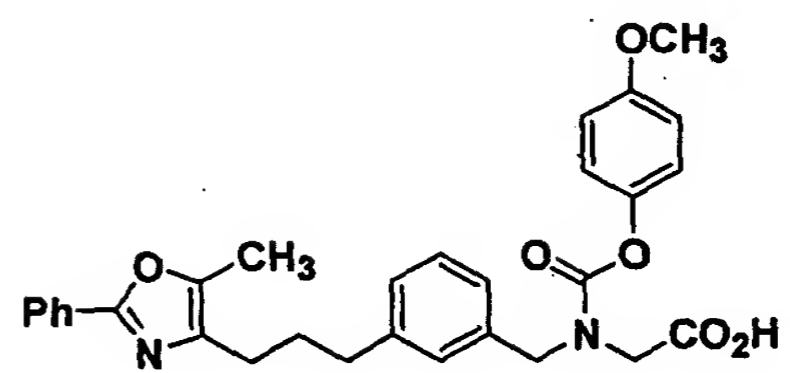
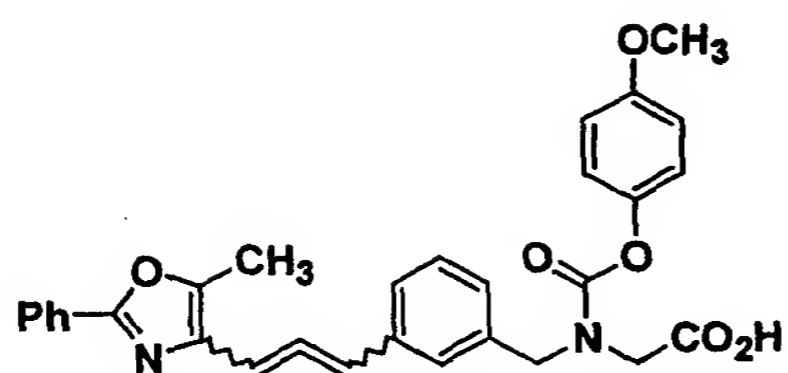




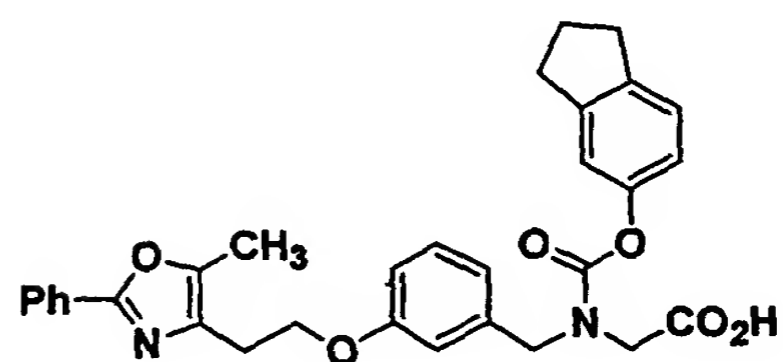
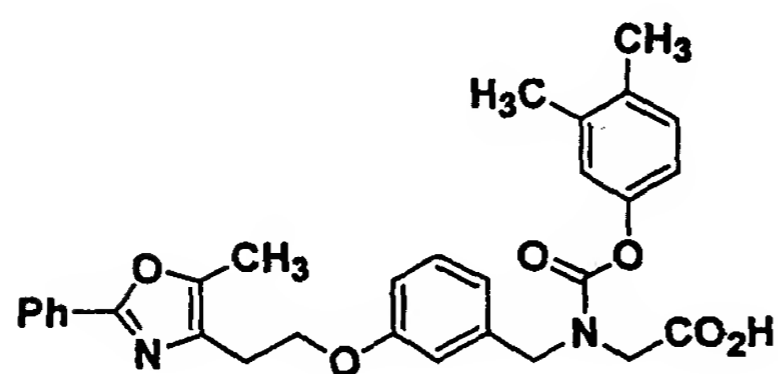


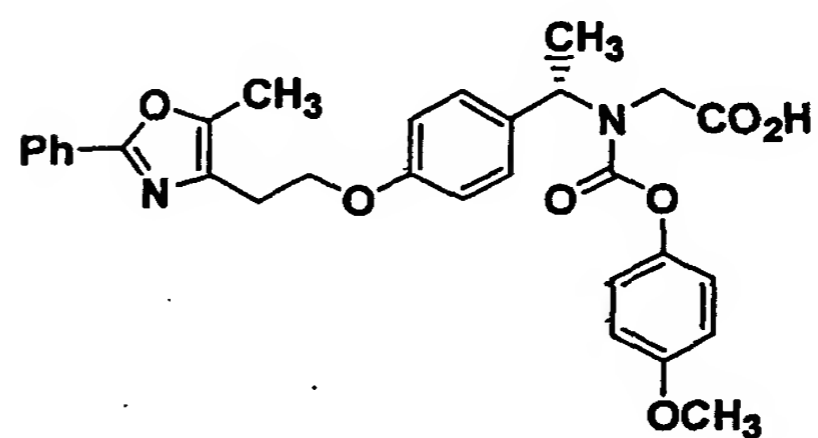
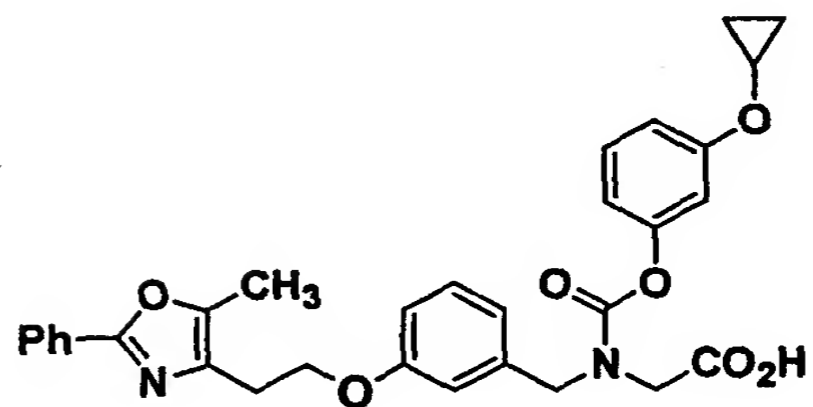
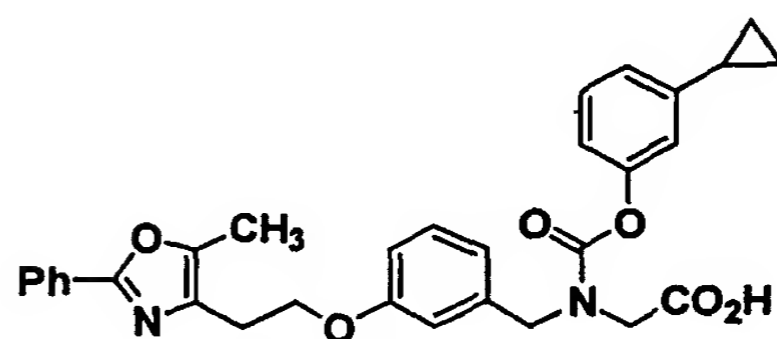
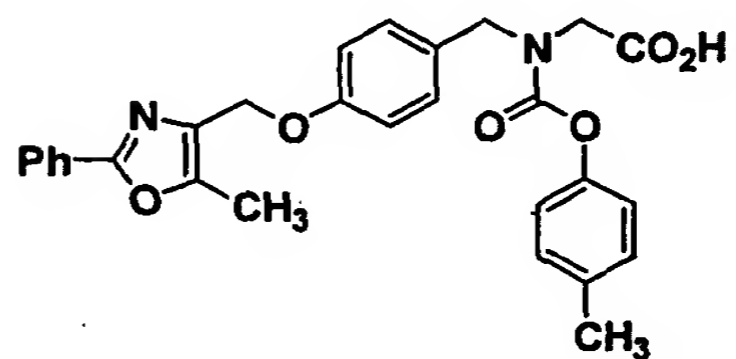
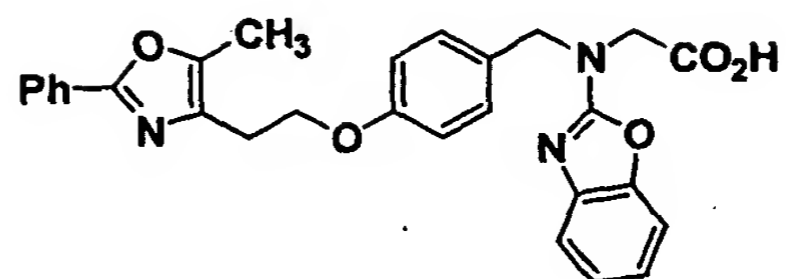


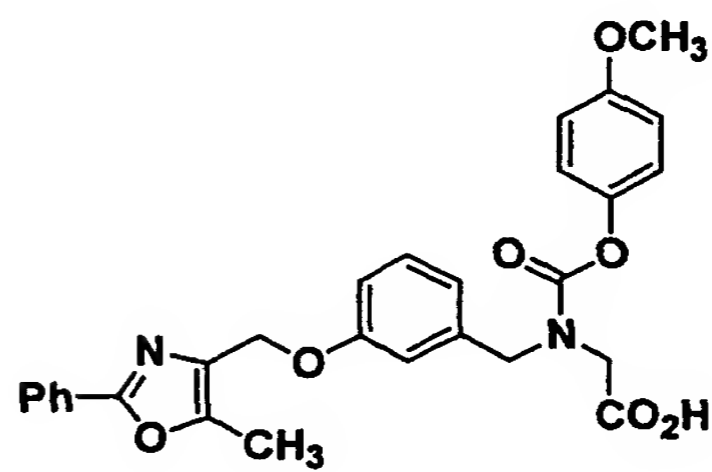
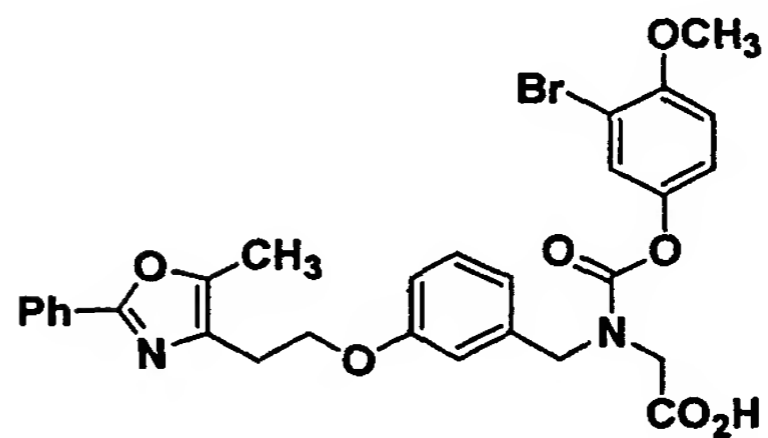
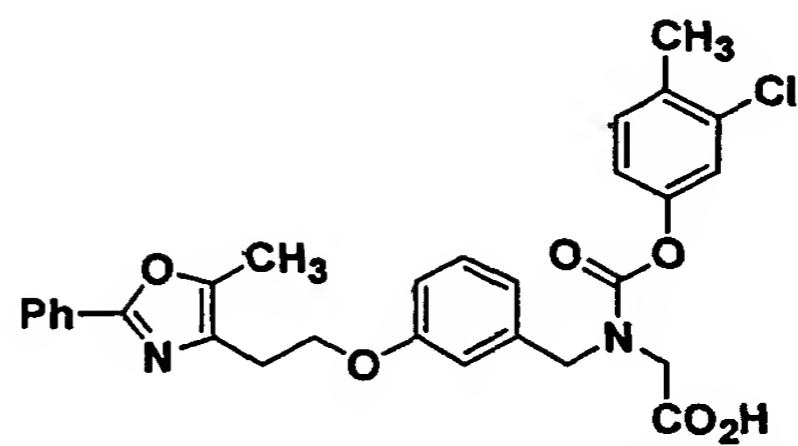




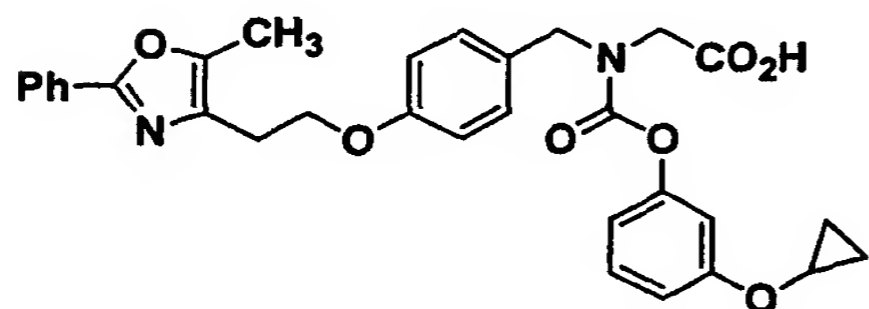
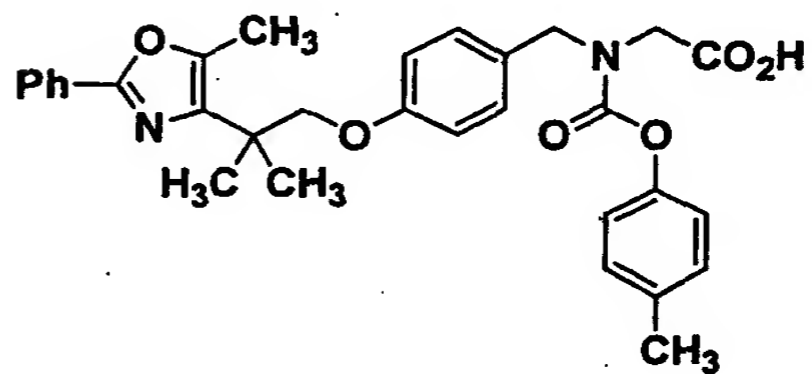
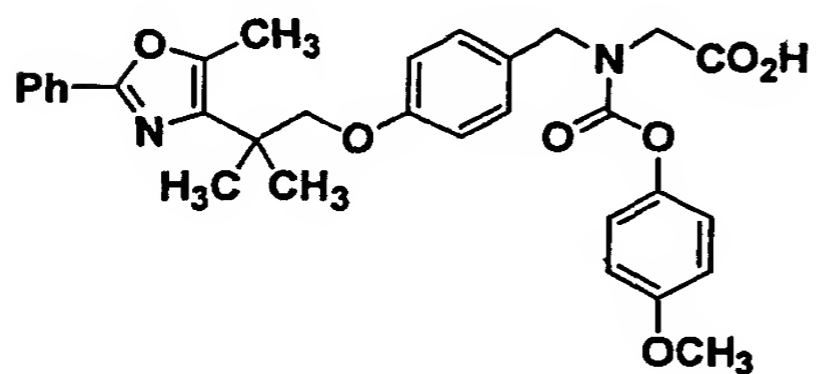
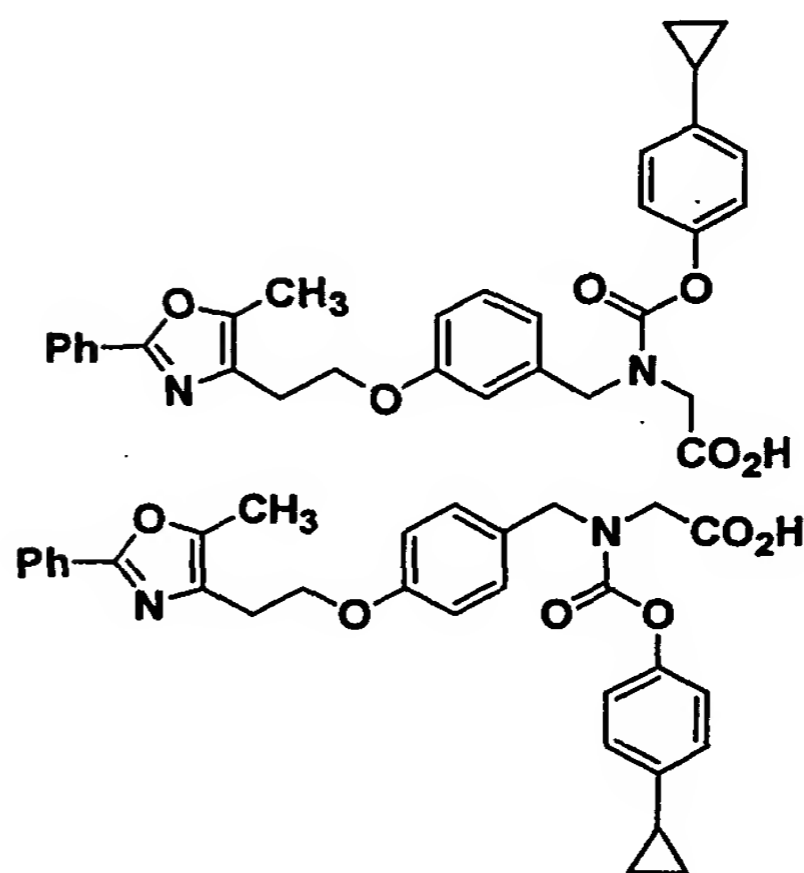
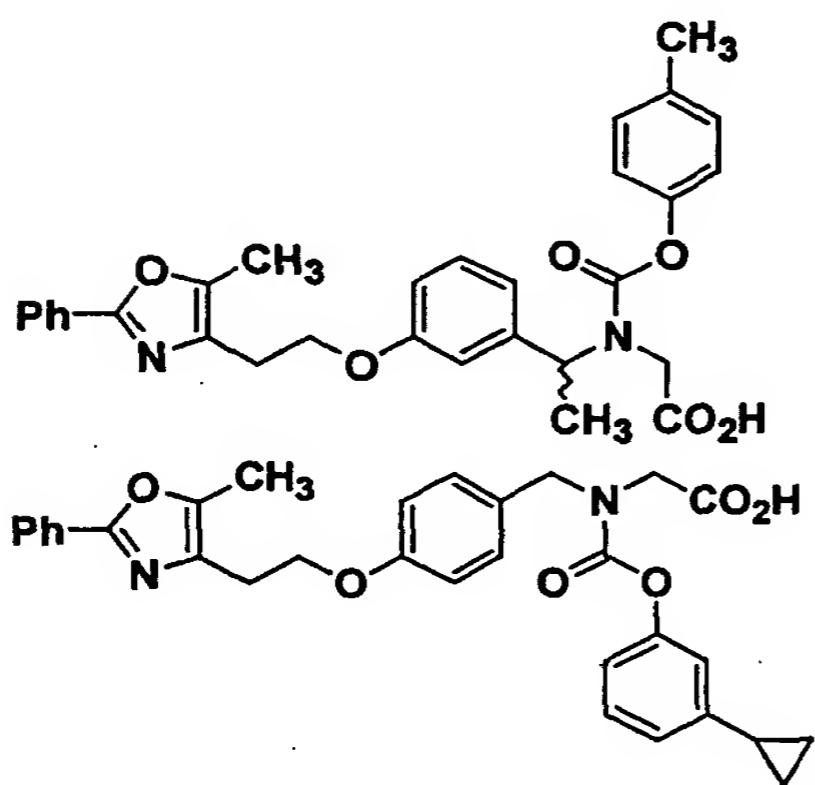
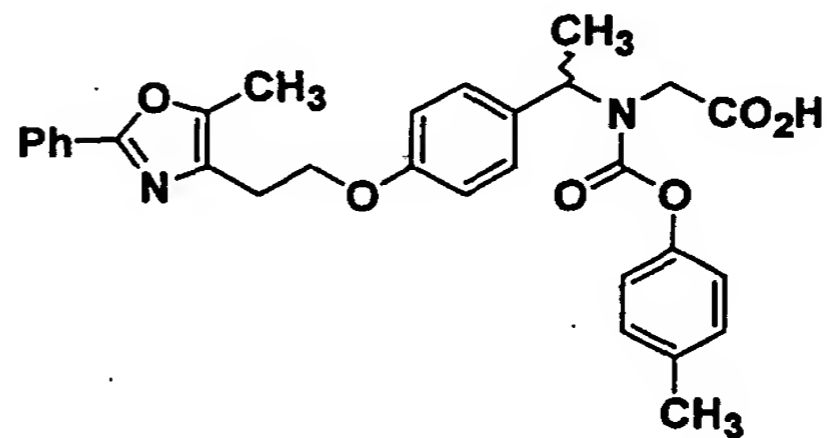
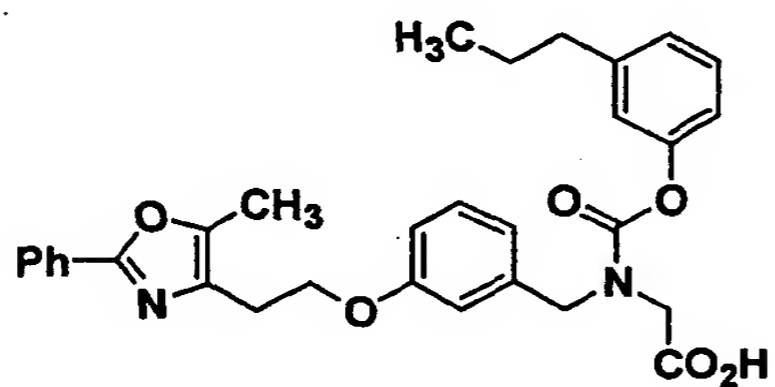
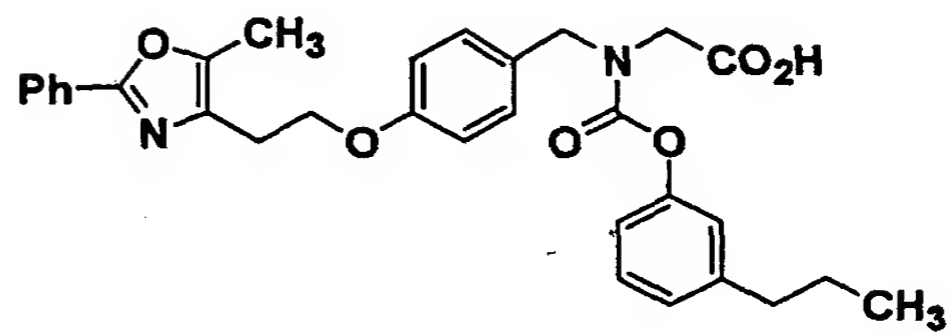
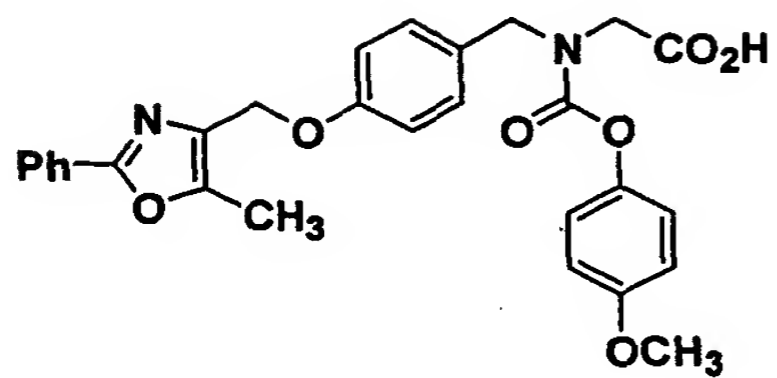
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In addition, in accordance with the present invention, a method is provided for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

In the above methods of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose



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Detailed Description of the Invention

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reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M.,
5 Protecting Groups in Organic Synthesis, 3rd Edition, 1999 [Wiley]).

Scheme 1 describes a general synthesis of the amino acids described in this invention. An alcohol II ($R^5(CH_2)_xOH$) (of which the most favored is 2-phenyl-5-methyl-oxazole-4-ethanol) is coupled with a hydroxy aryl-
10 or heteroaryl- aldehyde III (preferably 3- or 4-hydroxybenzaldehyde) under standard Mitsunobu reaction conditions (e.g. Mitsunobu, O., *Synthesis*, 1981, 1). The resulting aldehyde IV is then subjected to reductive
15 amination using procedures known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an α -amino ester hydrochloride V. PG in Scheme 1 denotes a preferred carboxylic acid protecting group, such as a methyl or tert-butyl ester. The resulting secondary
20 amino-ester VI is then subjected to a second reductive amination using methods known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an R^{3a} aldehyde VII. Final deprotection of the carboxylic acid ester under standard conditions known in the
25 literature (Greene) utilizing basic conditions (for methyl esters) or acidic conditions (for tert-butyl esters) then furnishes the desired amino acid products ID.

An alternative route to the aldehyde IV is shown in
30 Scheme 1A. The alcohol II ($R^5(CH_2)_xOH$) (of which the most favored is 2-[2-phenyl-5-methyl-oxazole-4-yl]-ethanol) is treated with methanesulfonyl chloride to give the corresponding mesylate VIII. The mesylate is then
alkylated under standard basic conditions with a
35 hydroxyaryl or hydroxyheteroaryl aldehyde III to furnish the aldehyde IV.

An alternative route to the amino acids IF is shown in Scheme 2. The secondary amino-ester VI is deprotected under standard conditions (basic conditions if the protecting group (PG) is methyl; acidic conditions if PG is tert-butyl) to furnish the corresponding amino acid IE. Reductive amination with an R^{3a} aldehyde under analogous conditions as described in Scheme 1 furnishes the desired tertiary amino acid products IF.

Alternatively, as shown in Scheme 3, the tertiary amino acids IF may also be obtained by alkylation of the secondary amino-ester VI with an alkylating agent IX (with an appropriate leaving group (LG) such as halide, mesylate, or tosylate) under standard conditions known in the art followed again by standard deprotection of the carboxylic acid ester X to provide the amino acids IF.

As shown in Scheme 4, the tertiary amino acid IF may also be assembled through reductive amination first of the R^{3a} aldehyde XI with an appropriate amine ester hydrochloride V. The resulting secondary amine-ester XII then is subjected to reductive amination with the appropriate alkyl, aryl or heteroaryl aldehyde IV (as in Scheme 1) followed by deprotection of the carboxylic acid ester to give the desired amino acid analogs IF.

For further substituted amino acids, a general synthetic scheme is shown in Scheme 5. Reductive amination of an appropriate amine XIII with an aryl or heteroaryl aldehyde XIV under standard conditions furnishes the corresponding secondary amine XV, which is then reacted with a halide-ester XVI (e.g. tert-butyl bromoacetate) to furnish the corresponding α -amino ester XVII. This amine-ester XVII is then deprotected under standard conditions to provide the desired amino acid analogs IF.

The synthetic route in Scheme 5 also provides a general scheme for the synthesis of the corresponding aminophosphonic acids IFA, as illustrated in Scheme 5a. The secondary amine XV is reacted with an appropriately

protected halide-phosphonate XVIA to provide the
corresponding aminophosphonate ester XVIIA, which is then
deprotected under standard conditions (Greene & Wuts) to
furnish the amino phosphonic acid IFA. Scheme 5b
5 illustrates the synthesis of the aminophosphinic acids
IFB, which again involves the reaction of an
appropriately protected halide-phosphinate ester XVIB
with the secondary amine XV. Deprotection of the
resulting aminophosphinate ester then provides the
10 phosphinic acid IFB.

An alternative to the sequence in Scheme 5 is shown
in Scheme 6. A hydroxyaryl or heteroaryl amine XVIII is
selectively protected on nitrogen to provide protected
amine XIX. A preferred $R^5(CH_2)_nOH$ (II) is then reacted
15 with XIX under Mitsunobu conditions to provide the
corresponding ether, followed by deprotection of the
amine, to form the free amine XX. The free amine XX is
then activated with a standard activating group (2,4-
dinitrobenzenesulfonamide; T. Fukuyama et al, *Tetrahedron*
20 *Lett.* **1997**, 38, 5831) and is then treated with an α -halo
ester XVI as in Scheme 5. The 2,4 dinitrobenzene-
sulfonamide XXI is deprotected under literature
conditions (T. Fukuyama et al, *Tetrahedron Lett.*, **1997**,
38, 5831) to furnish a secondary α -amino-ester XXII which
25 is then subjected to a reductive amination with an R^{3a}
aldehyde XI followed by deprotection of the ester X to
furnish the desired analogs IF.

Scheme 7 describes an alternative general route to
the amino acid analogs IG. A hydroxyaryl or heteroaryl
30 aldehyde III is subjected to the usual reductive
amination conditions with an appropriate amine-ester
hydrochloride V. The resulting secondary amine-ester
XXIII is functionalized, in this case by a second
reductive amination with an R^{3a} aldehyde VII to furnish
35 the corresponding hydroxy tertiary amine-ester XXIV.
This can now undergo a Mitsunobu reaction with a
preferred alcohol II ($R^5(CH_2)_nOH$) which followed by

deprotection of the ester XXV furnishes the desired analogs IG.

- Scheme 8 describes a general synthesis of diaryl and aryl-heteroaryl-substituted amino acid analogs IH.
- 5 The secondary amine-ester XXII undergoes reductive amination with an appropriately substituted formyl phenyl boronic acid XXVI under standard conditions to give the corresponding tertiary amine-ester boronic acid XXVII. The aryl boronic acid XXVII can then undergo a Suzuki
- 10 coupling (e.g. conditions as described in Gibson, S. E., *Transition Metals in Organic Synthesis, A Practical Approach*, pp. 47-50, 1997) with aryl or heteroaryl halides XXVIII (especially bromides) to furnish the appropriate cross-coupling diaryl products XXIX.
- 15 Deprotection of the amine-ester XXIX generates the desired amino acid analogs IH.

- Scheme 9 describes a general synthesis of diaryl and aryl-heteroaryl ether-substituted amino acid analogs IJ. The tertiary amine-ester boronic acid XXVII which is
- 20 described in Scheme 8 can be coupled with appropriately substituted phenols XXX under literature conditions (D. A. Evans et al, *Tetrahedron Lett.*, 1998, 39, 2937) to furnish the appropriate diaryl or aryl-heteroaryl ethers XXXI, which after deprotection afford the desired amino
- 25 acid analogs IJ.

- Alternatively, as shown in Scheme 10, reductive amination of the secondary amine-ester XXII with an appropriately substituted hydroxyaryl or hydroxyheteroaryl aldehyde XXXII furnishes the
- 30 corresponding phenol-tertiary amine-ester XXXIII. The phenol XXXIII can then undergo coupling with appropriate aryl or heteroaryl boronic acids XXXIV under literature conditions (D. A. Evans et al, *Tetrahedron Lett.*, 1998, 39, 2937) to furnish the corresponding diaryl or
- 35 arylheteroaryl ether-amino esters XXXI. The desired analogs IJ are then obtained after deprotection of the amine-ester XXXI.

Scheme 11 illustrates the synthesis of the carbamate-acid analogs IK. The secondary amine-ester XXII can be reacted with appropriate chloroformates XXXV under standard literature conditions (optimally in CH_2Cl_2 or CHCl_3 in the presence of a base such as Et_3N) to furnish the corresponding carbamate-esters. The requisite analogs IK are then obtained after deprotection of the carbamate-ester. Alternatively, the secondary amine-ester XXII can be reacted with phosgene to generate the corresponding carbamyl chloride XXXVI. This carbamyl chloride intermediate XXXVI can be reacted with $\text{R}^{3a}\text{-OH}$ (XXXVII) (optimally substituted phenols) to afford the corresponding carbamate-acids IK after deprotection.

Scheme 12 illustrates the further functionalization of aryl carbamate-acid analogs IK. The secondary amine-ester XXII is reacted with an aryl chloroformate XXXVIII (containing a protected hydroxyl group) to form XXXIX. The hydroxyl group is then selectively deprotected in the presence of the ester functionality to provide XL, then alkylated with an appropriate $\text{R}^6\text{-LG}$ (XLI) (where LG is halide, mesylate or tosylate, and R^6 is most preferably $\text{CHF}_2\text{-}$, or $\text{CH}_3\text{CH}_2\text{-}$) in the presence of base. Deprotection of the ester then furnishes the desired carbamate-acid analogs IL.

The secondary amine-ester XXIIA can be functionalized with substituted aryl or aliphatic carboxylic acids XLII, under standard peptide coupling conditions, as illustrated in Scheme 13. The amide bond-forming reactions are conducted under standard peptide coupling procedures known in the art. Optimally, the reaction is conducted in a solvent such as DMF at 0°C to RT using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC or EDCI or WSC), 1-hydroxybenzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT) and a base, for example Hunig's base (diisopropylethylamine), N-methyl morpholine or triethylamine. Deprotection of the amide-ester then furnishes the desired amide-acid analogs IM.

30 Scheme 18 describes a general synthesis of the
hydrazide-acid analogs IS. A substituted aryl carboxylic
acid 1 is treated with methanesulfonyl chloride in the
presence of base; the intermediate is then reacted with a
protected hydrazine-ester VA to give the corresponding
35 acylated hydrazine 1a (ref: *Synthesis*, 1989, 745-747).
The acylhydrazine 1a is coupled with an appropriately
substituted aryl aldehyde IV under reductive amination


conditions to give the corresponding protected hydrazide ester 3 (ref: *Can. J. Chem.*, 1998, 76, 1180-1187).

Deprotection of the ester 3 then furnishes the hydrazide-acid analogs IS.

5 An alternative synthetic approach to hydrazide-acids IS is shown in Scheme 19. An aryl aldehyde IV can be reduced to the corresponding alcohol under standard conditions (e.g. NaBH_4). This alcohol is then converted to the corresponding bromide 4 using standard conditions
10 (e.g. $\text{Ph}_3\text{P/CBr}_4$ or PBr_3). The bromide 4 is then reacted with the hydrazine-ester 1a (ref: *Tetrahedron Lett.*, 1993, 34, 207-210) to furnish the protected hydrazide-ester 3, which is then deprotected to give the hydrazide-acid analogs IS.

15 The different approaches to the preparation of the α -alkylbenzyl amino acid and carbamate-acid analogs IT and IU are exemplified in the following synthetic schemes. In Scheme 20 an appropriately substituted aryl aldehyde IV is treated with a suitable organometallic
20 reagent (e.g. a Grignard reagent R^{10}MgBr) under standard conditions to give the corresponding secondary alcohol, which is then oxidized under standard conditions (e.g. Swern oxidation with $(\text{COCl})_2/\text{DMSO}/\text{Et}_3\text{N}$ or using pyridinium chlorochromate) to give the corresponding ketone 5.

25 Reductive amination of the ketone 5 with an appropriately substituted amino-ester 6 provides the corresponding α -alkylbenzyl amino-ester 7. It will be understood that in

the amino ester 6, the moiety  does not necessarily represent two repeating units.

30 Acylation of amino-ester 7 with an appropriately substituted aryl or heteroaryl chloroformate XXXV followed by deprotection provides the racemic carbamate-acid analogs IT. Reductive amination of alkylbenzyl amino-ester 7 with aryl aldehyde VII followed by
35 deprotection provides the racemic amino-acid analogs IU.

Alternatively, as shown in Scheme 21, asymmetric reduction (e.g. using the Corey oxazaborolidine reduction protocol; review: E. J. Corey & C. Helal, *Angew. Chem. Int. Ed. Engl.*, 1998, 37, 1986-2012.) of the aryl-ketone 5 provides each of the desired enantiomeric alcohols 8 (although only one enantiomer is represented in the scheme). Treatment of the chiral alcohol 8 with azide in a Mitsunobu-like reaction (ref: A. S. Thompson et. al., *J. Org. Chem.* 1993, 58, 5886-5888) gives the corresponding chiral azide (with inverted stereochemistry from the starting alcohol). The azide is then converted to the amine 9 by standard reduction methods (e.g. hydrogenation or $\text{Ph}_3\text{P}/\text{THF}/\text{H}_2\text{O}$). Treatment of the chiral amine 9 with an ester XVIA (containing an appropriate leaving group) provides the secondary amino-ester 10. Acylation of amino-ester 10 with an aryl or heteroaryl chloroformate XXXV followed by deprotection provides the chiral carbamate-acid analogs ITa (which may be either enantiomer depending upon the stereochemistry of 8). Reductive amination of alkyl amino-ester 10 with aryl aldehydes VII followed by deprotection provides the chiral amino-acid analogs IUA (which may be either enantiomer depending upon the stereochemistry of 8).

An alternative to Scheme 21 is shown in Scheme 22. An appropriately protected oxyaryl ketone 11 undergoes asymmetric reduction to give the chiral alcohol 12. This is converted to the chiral amine 13 via the identical sequence as in Scheme 21 (via the chiral azide). Treatment of the chiral amine 13 with an ester XVIA (LG = halogen or mesylate) gives the corresponding secondary amino-ester 14. Acylation of 14 with an aryl or heteroaryl chloroformate XXXV provides the corresponding carbamate-ester. Selective deprotection furnishes the free phenol carbamate-ester 15. Alkylation of the phenol 15 with a halide or mesylate VIII followed by deprotection provides the carbamate-acid analogs ITa. An analogous sequence (involving reductive amination of the

secondary amino-ester 14 with an aryl or heteroaryl aldehyde VII, then selective deprotection, alkylation with VIII and a final deprotection) provides the amino acid analogs IUa.

5 It will be appreciated that either the (R)- or (S)- enantiomer of ITa or IUa may be synthesized in Schemes 21 and 22, depending upon the chirality of the reducing agent employed.

A fourth synthetic sequence is shown in Scheme 23. The substituted aldehyde IV is condensed with an amino-ester hydrochloride 6 to give the corresponding imine 16, which is then treated in situ with an appropriately substituted allylic halide 17 in the presence of indium metal (reference: Loh, T.-P., et al., *Tetrahedron Lett.*, 1997, 38, 865-868) to give the α -allyl benzyl amino-ester 18. Acylation of amine 18 with an aryl or heteroaryl chloroformate XXXV followed by deprotection provides the carbamate-acid analogs IV. Reductive amination of alkyl amino-ester 18 with an aryl or heteroaryl aldehyde VII followed by deprotection provides the amino-acid analogs IW.

Scheme 24 shows the preparation of the required intermediate 2-aryl-5-methyl-oxazol-4-yl methyl chloride 21 (following the general procedure described in Malamas, M. S., et al, *J. Med. Chem.*, 1996, 39, 237-245). A substituted aryl aldehyde 19 is condensed with butane-2,3-dione mono-oxime under acidic conditions to give the corresponding oxazole N-oxide 20. Deoxygenation of the oxazole N-oxide 20 with concomitant chlorination furnishes the desired chloromethyl aryl-oxazoles 21. Hydrolysis of chloromethyl oxazole 21 under basic conditions furnishes the corresponding oxazole-methanol 22. Oxidation of alcohol 22 to the corresponding aldehyde is followed by conversion to the corresponding dibromoalkene 23 (e.g. $\text{Ph}_3\text{P/CBr}_4$). The dibromide 23 is converted to the corresponding alkynyl-lithium species (using an organolithium reagent such as *n*-BuLi), which

can be reacted in situ with an appropriate electrophile such as formaldehyde to give the corresponding acetylenic alcohol (ref: Corey, E. J., et al., *Tetrahedron Lett.* 1972, 3769, or Gangakhedkar, K. K., *Synth. Commun.* 1996, 26, 1887-1896). This alcohol can then be converted to the corresponding mesylate 24 and alkylated with an appropriate phenol 25 to provide analogs IX. Further stereoselective reduction (e.g. H₂/Lindlar's catalyst) provides the E- or Z- alkenyl analogs IY.

10 Scheme 25 describes a general synthesis of the
amino-benzoxazole analogs IZ (general ref: Sato, Y., et
al, *J. Med. Chem.* 1998, 41, 3015-3021). An appropriately
substituted ortho-aminophenol 26 is treated with CS₂ in
the presence of base to furnish the corresponding
15 mercapto-benzoxazole 27. Treatment of this thiol 27 with
an appropriate chlorinating agent (e.g. PCl₅) provides the
key intermediate chlorobenzoxazole 28, which is reacted
with the secondary amino-ester VI to furnish, after
deprotection, the amino benzoxazole-acid analogs IZ.

20 The thiazole analogs IZa were synthesized according
to the general synthetic route outlined in Scheme 26
(ref. Collins, J. L., et al., *J. Med. Chem.* 1998, 41,
5037). The secondary amino-ester XXIII is reacted with
an aryl or heteroaryl chloroformate XXXV in the presence
25 of an appropriate base (e.g. pyridine or triethylamine)
to furnish the corresponding hydroxyaryl carbamate-ester
29. The hydroxyaryl ester 29 is then reacted with an
appropriately substituted α -bromo vinyl ketone 29a (for S₃
= CH₃, e.g. Weyerstahl, P., et. al., *Flavour Fragr. J.*,
30 1998, 13, 177 or Sokolov, N. A., et al., *Zh. Org. Khim.*,
1980, 16, 281-283) in the presence of an appropriate base
(e.g. K₂CO₃) to give the corresponding Michael reaction
adduct, the α -bromoketone carbamate-ester 30. The α -
bromoketone 30 is then subjected to a condensation
35 reaction with an appropriately substituted aryl amide 31
(A = O) or aryl thioamide 31 (A = S) to furnish either
the corresponding oxazole (from the amide) or the

thiazole (from the thioamide) (ref: Malamas, M. S., et al, *J. Med. Chem.*, 1996, 39, 237-245). Finally, deprotection of esters 31 then provides the substituted oxazole and thiazole carbamate acid analogs 1Za.

5 It will be appreciated that in the following
schemes where the carbamate-acid analogs are prepared,
the corresponding amino acid analogs may also be prepared
by replacing the chloroformate reaction with an aldehyde
in a reductive amination reaction (as in Scheme 20 with
10 intermediate amine 7).

Scheme 27 describes a general synthesis of the acids IZb and IZc. A halo-substituted aryl aldehyde 32 (preferably iodide or bromide) is subjected to reductive amination using procedures known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an α -amino acid ester hydrochloride V. The resulting secondary amino-ester 33 is then reacted with an aryl or heteroaryl chloroformate XXXV in the presence of an appropriate base (e.g. pyridine or triethylamine) to furnish the corresponding halo-aryl carbamate-ester 34. Aryl halide 34 is then reacted with an appropriate aryl- or heteroaryl-substituted acetylene 35 (the preferred acetylene being 5-phenyl-2-methyl-oxazol-4-yl-methylacetylene) in the presence of an appropriate palladium catalyst (e.g. $(\text{Ph}_3\text{P})_2\text{PdCl}_2$) and a copper (I) salt (e.g. CuI) in a Sonogashira coupling reaction (ref: *Organocopper Reagents, a Practical Approach*, R. J. K. Taylor, Ed., Chapter 10, pp 217-236, Campbell, I. B., Oxford University Press, 1994) to furnish the key intermediate, arylacetylene carbamate ester 36.

The arylacetylene ester 36 is deprotected to provide the corresponding arylacetylene acid analogs 1Zb. The acetylene moiety of 36 can be reduced by standard methods (e.g. hydrogenation, ref: M. Hudlicky, 35 Reductions in Organic Chemistry, 2nd Edition, ACS, 1996, Chapter 1) to furnish the corresponding fully saturated

Stereoselective reduction of the acetylene ester 36 by standard methods (e.g. Lindlar's catalyst; ref:

Williams, Ed., Chapter 6, pp 117-136, Oxford University Press, 1996) can be achieved to provide the corresponding cis-alkenyl aryl carbamate-ester, which is then deprotected to furnish the Z-alkenyl aryl carbamate acid analogs 1Zd (Scheme 28). Alternatively, this sequence can be reversed, i.e. the initial step being the deprotection of acetylenic ester 36 to the acetylenic acid, followed by stereoselective reduction of the acetylene moiety to provide the Z-alkene-acid analogs

The corresponding trans-alkenyl aryl carbamate acids 1Ze can be synthesized according to the general route in Scheme 29. An aryl- or heteroaryl-acetylene 35 (the preferred moiety again being 5-phenyl-2-methyl-oxazol-4-yl-methylacetylene) is halogenated under standard conditions (ref: Boden, C. D. J. et al., *J. Chem. Soc. Perkin Trans. I*, 1996, 2417; or Lu, W. et al., *Tetrahedron Lett.* 1998, 39, 9521) to give the corresponding halo-acetylene, which is then converted to the corresponding trans-alkenyl stannane 37 (ref: Boden, C. D. J., *J. Chem. Soc., Perkin Trans. I*, 1996, 2417). This aryl- or heteroaryl-substituted trans-alkenyl stannane 37 is then coupled with the halo-aryl carbamate ester 34 under standard Stille coupling conditions (ref: Farina, V. et al., "The Stille Reaction", *Organic Reactions*, 1997, 50, 1) to furnish the corresponding trans-alkenyl aryl carbamate ester 38. This carbamate-ester is then deprotected under standard conditions to give the desired trans-alkenyl aryl carbamate acid analogs 1Ze.

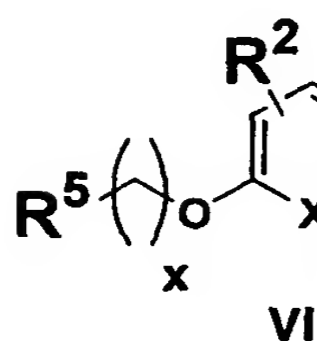
The corresponding cyclopropyl analogs IZf and IZg are synthesized according to Scheme 30. For the cis- or

(Z-) cyclopropyl analogs, stereoselective reduction (H_2 /Lindlar's catalyst) of the alkynyl moiety of intermediate alkynyl ester 36 (as for analogs IZd), followed by cyclopropanation under standard conditions (Zhao, Y., et al, *J. Org. Chem.* 1995, 60, 5236-5242) and finally deprotection provides the cis-cyclopropyl carbamate-acid analogs IZf. For the trans-cyclopropyl analogs IF, analogous cyclopropanation of the E-alkene moiety of intermediate 38 followed by deprotection provides the trans-cyclopropyl carbamate-acid analogs IZg.

A preferred alternative asymmetric synthesis of ITa (Scheme 21) is shown in Scheme 31. Protection of a chiral amine 39 (with the phenol protected), preferably as a carbamate, provides intermediate 40. Removal of the phenolic protecting group of 40 provides the free phenol 41. Alkylation of phenol 41 with the mesylate VIII furnishes the protected amine 42. Deprotection of this amine then furnishes the key intermediate secondary amino-ester 9, which is then carried on to analogs ITa and IUa according to Scheme 21.

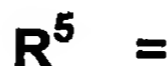
A preferred asymmetric synthesis of analogs IIA is shown in Scheme 32. The aldehyde IV is subjected to standard Wittig reaction conditions (ref: Preparation of Alkenes, a Practical Approach, J. J. Williams, Ed., Chapter 2, pp 19-58) to furnish the alkene 43. Asymmetric aminohydroxylation according to known literature procedures (ref: O'Brien, P., *Angew. Chem. Int. Ed.*, 1999, 38, 326 and Reddy, K. L., and Sharpless, K. B., *J. Am. Chem. Soc.*, 1998, 120, 1207) furnishes the desired amino-alcohol 44 as a single enantiomer. Selective protection of the amine provides the alcohol 45. Alcohol 45 is then converted to the intermediate 46, which contains a suitable leaving group (either a halide or a mesylate) for the subsequent cuprate reaction. Reaction of an appropriate higher-order cuprate (ref: L. A. Paquette, Ed., *Organic Reactions*, 1992, Vol. 41, J. Wiley & Sons) with the protected amine substrate 46

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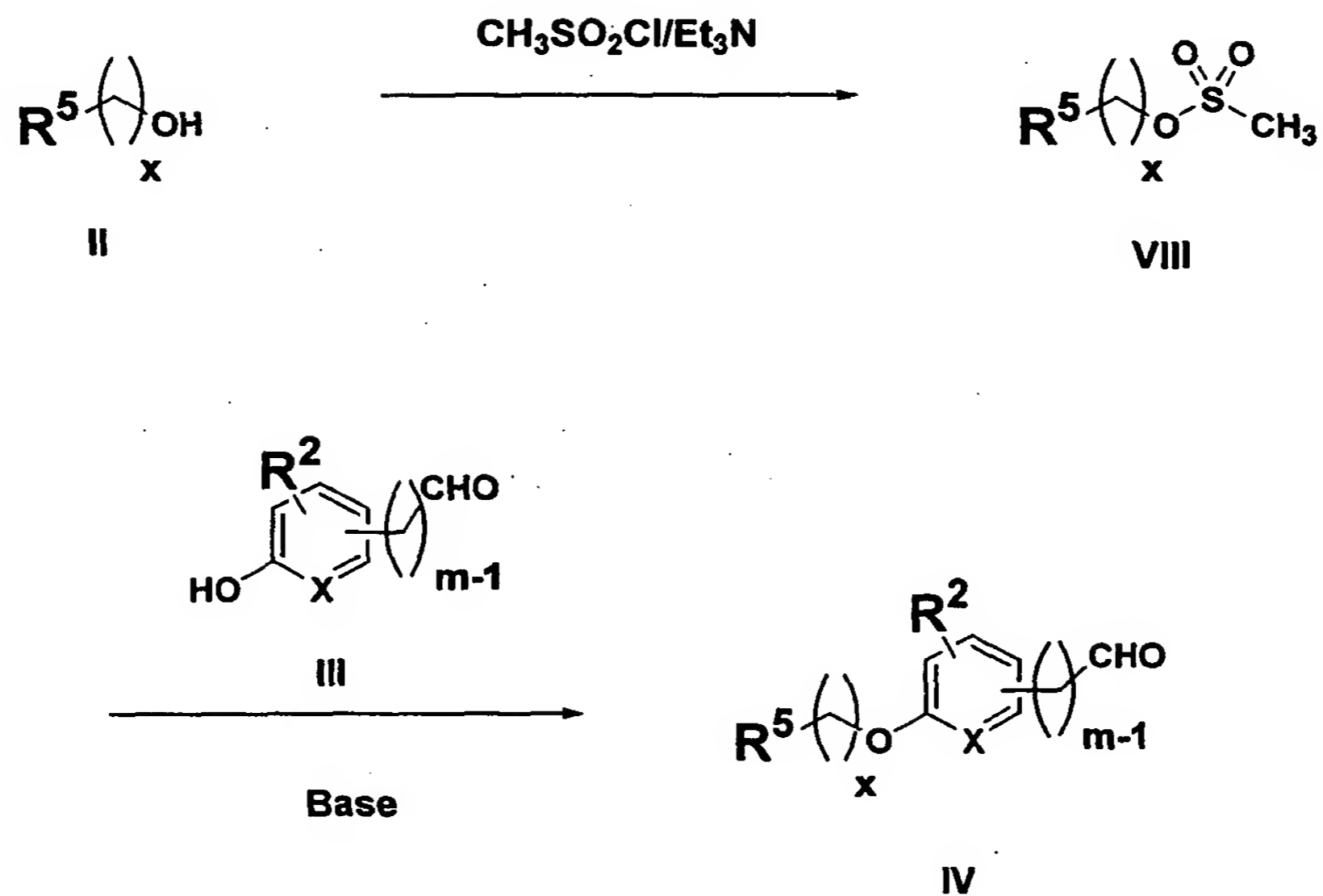


Scheme 1

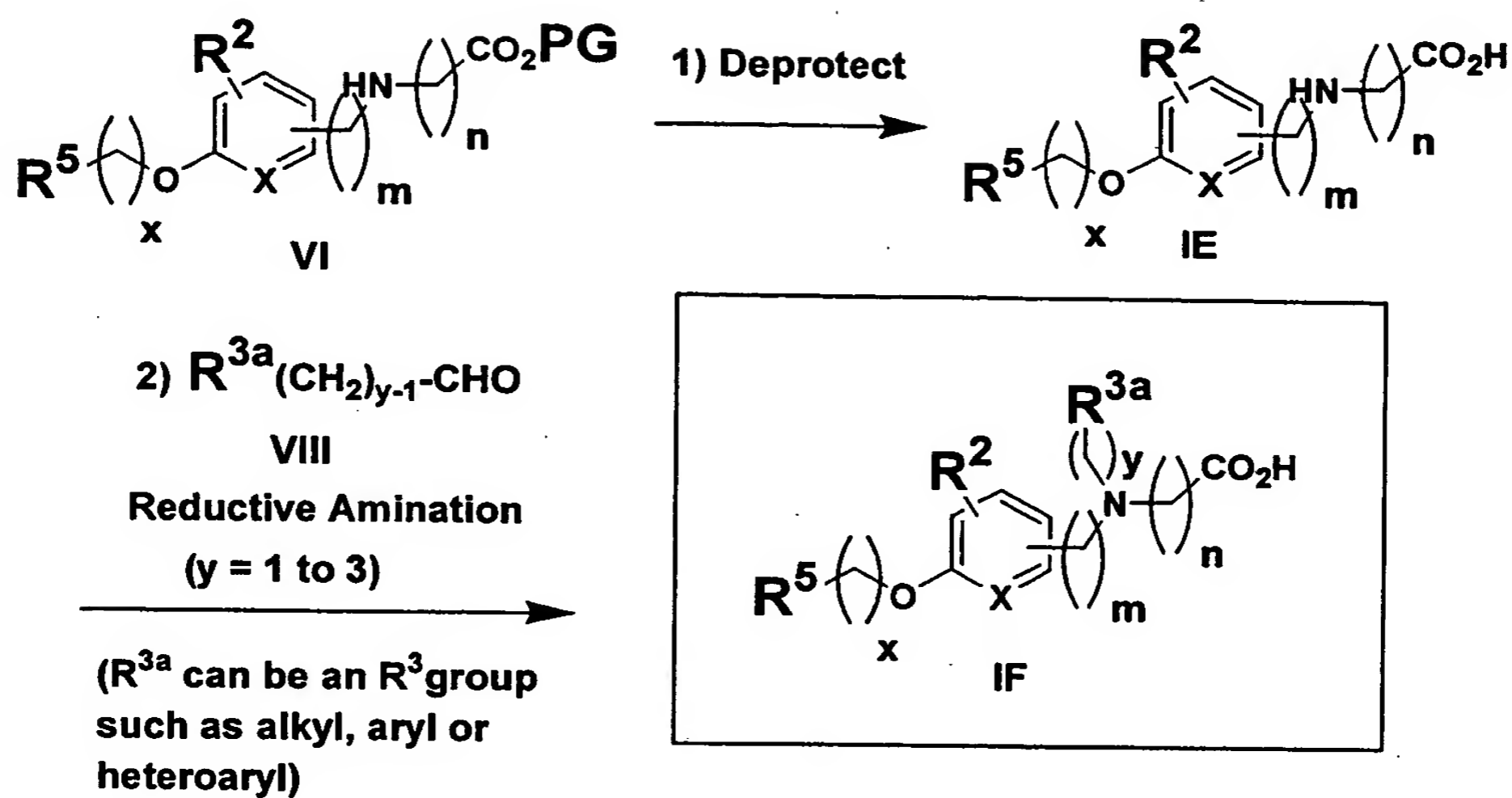
In this and the following Reaction Schemes:



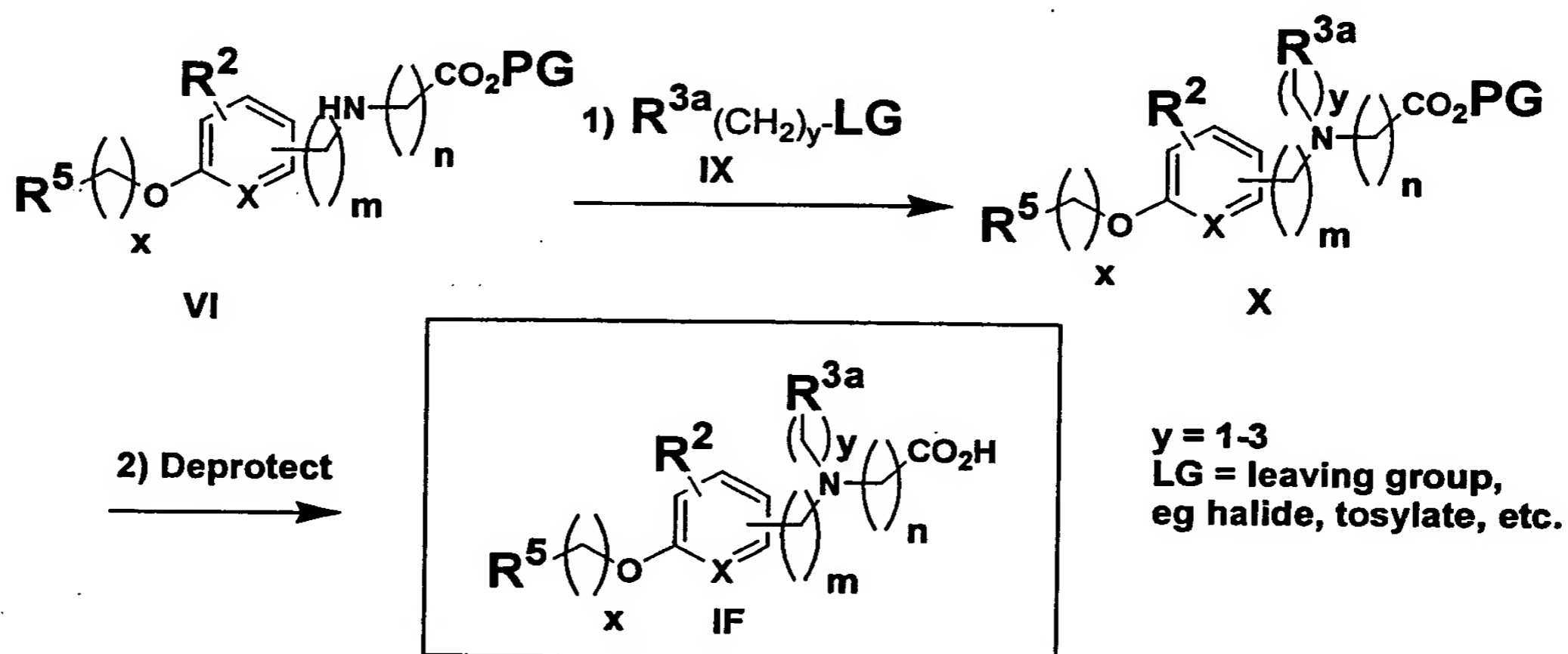
Alternative Scheme 1A for Preparing Aldehyde IV



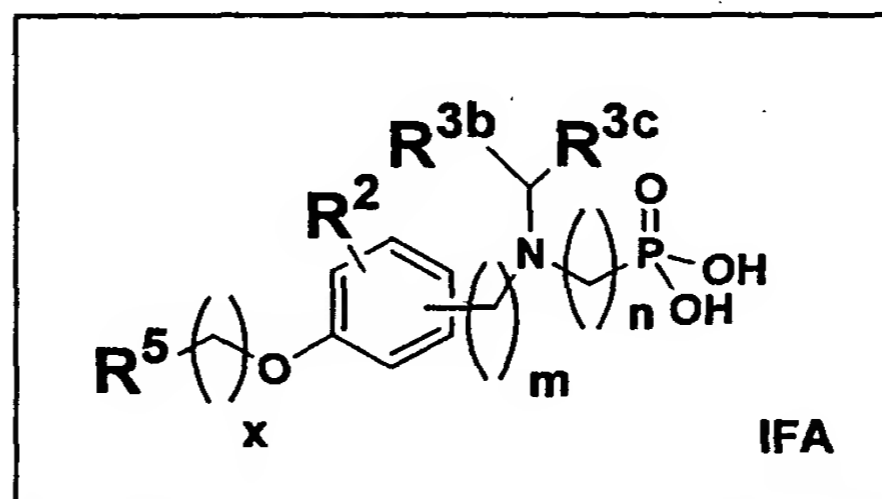
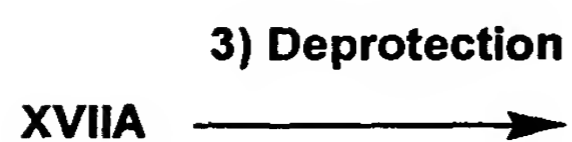
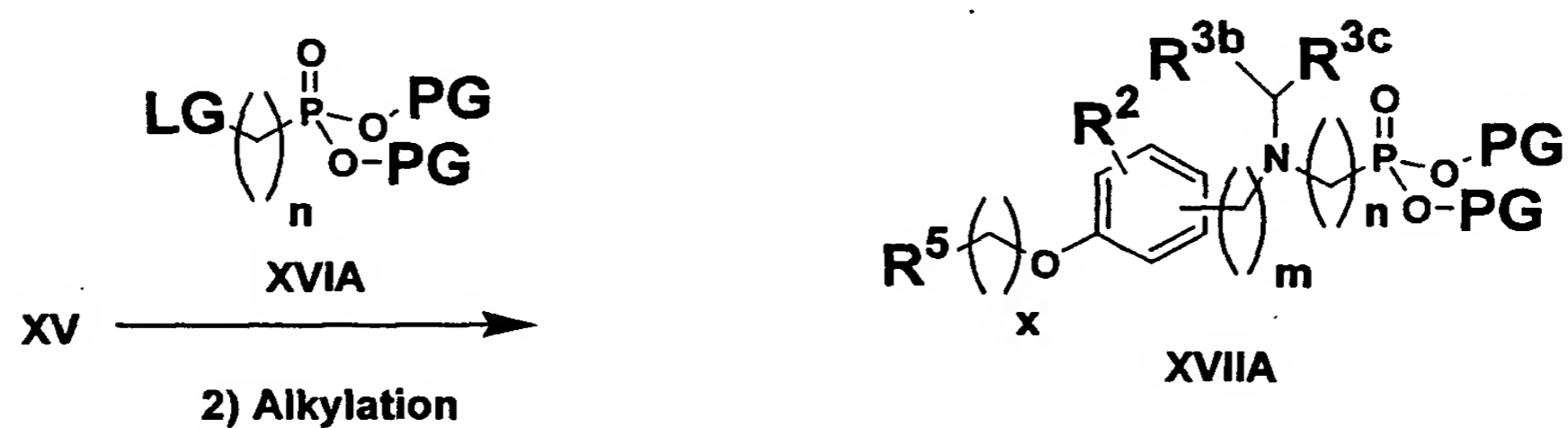
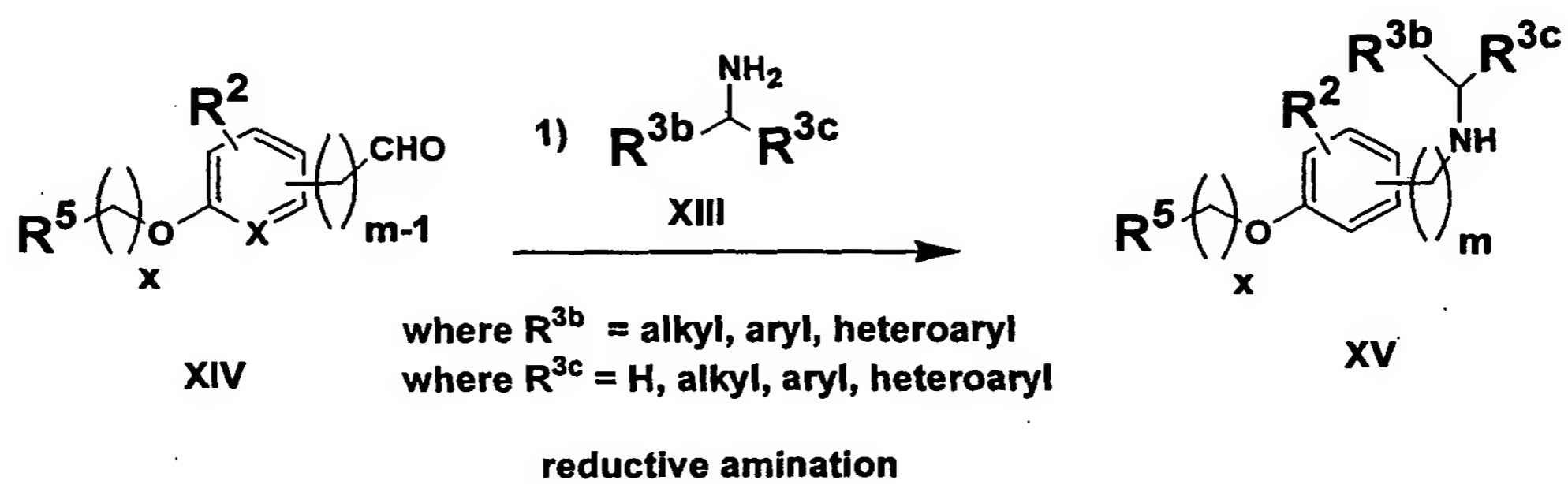
SCHEME 1A



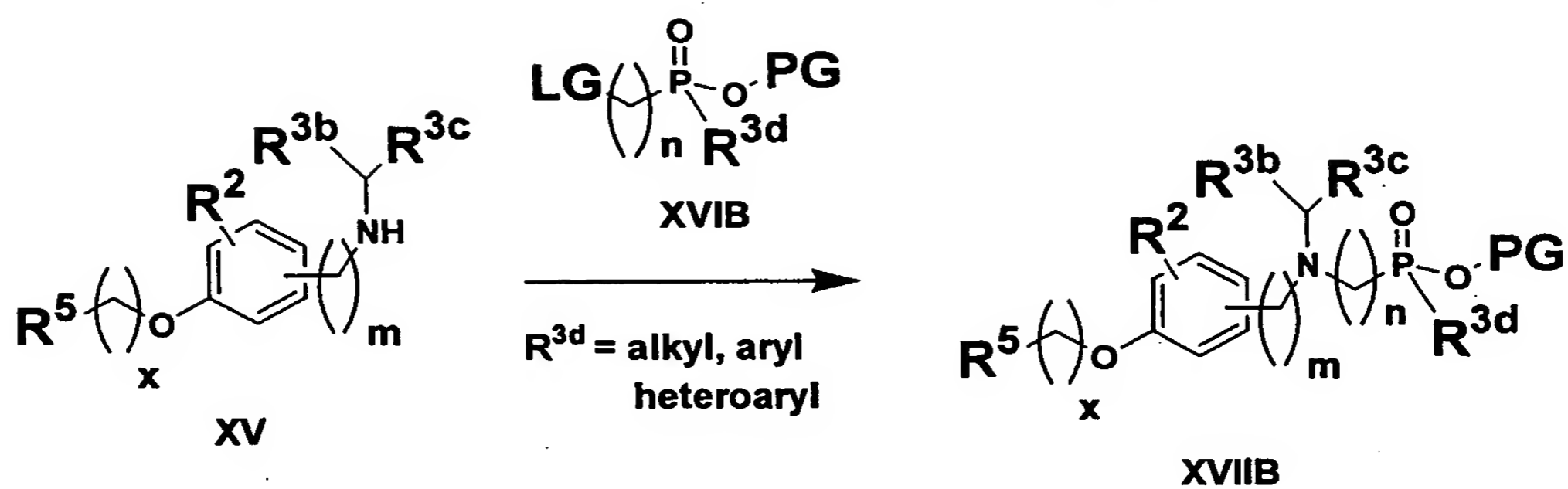
Scheme 2



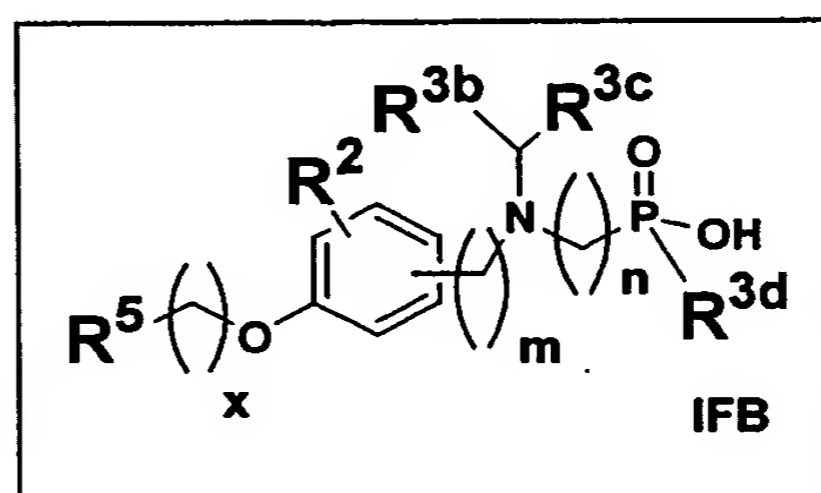
Scheme 3



Scheme 5a

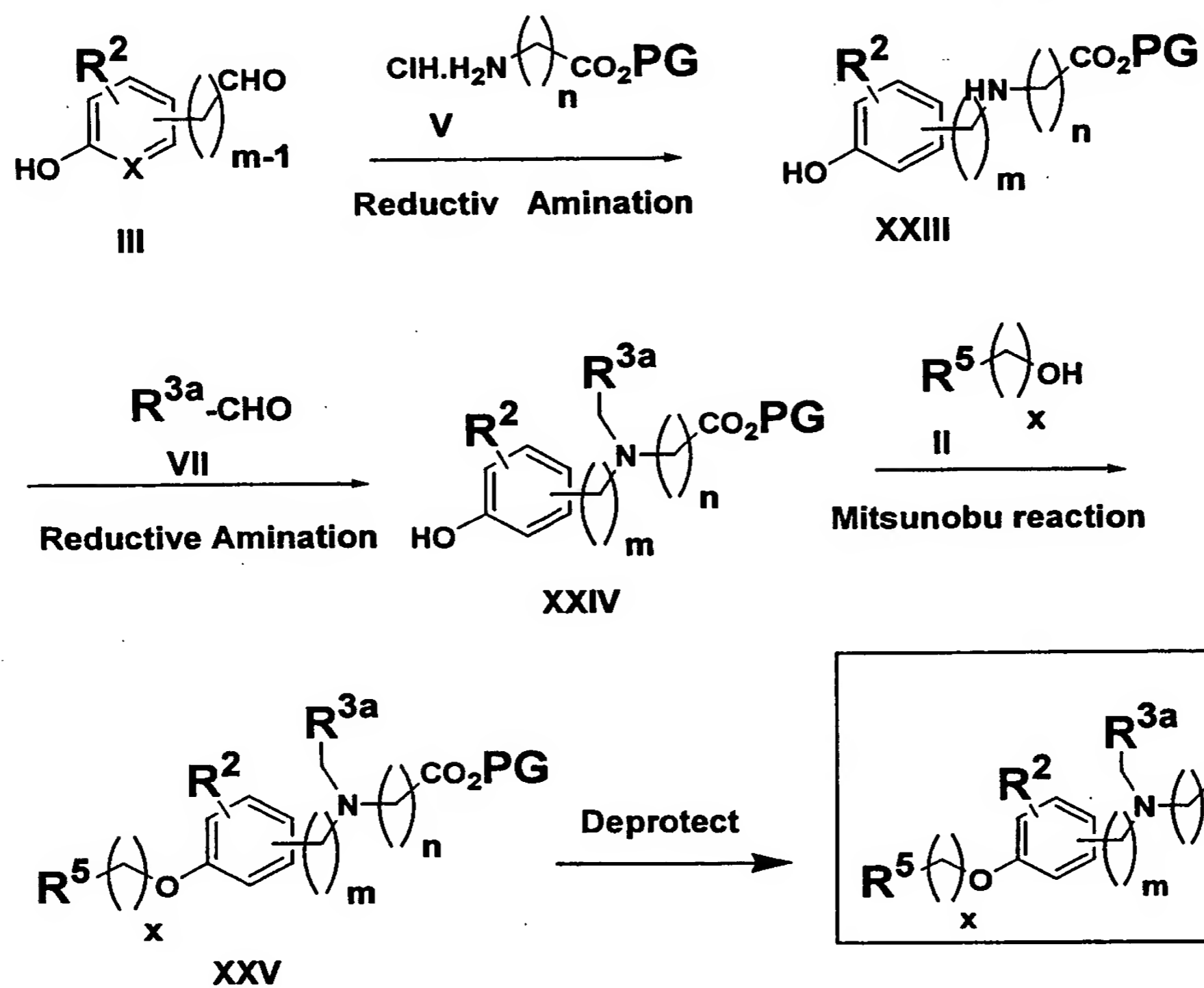


Deprotection

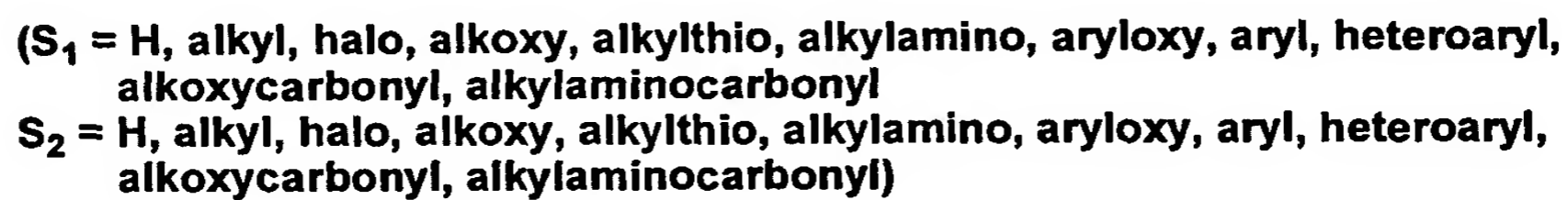


Scheme 5b





Scheme 7

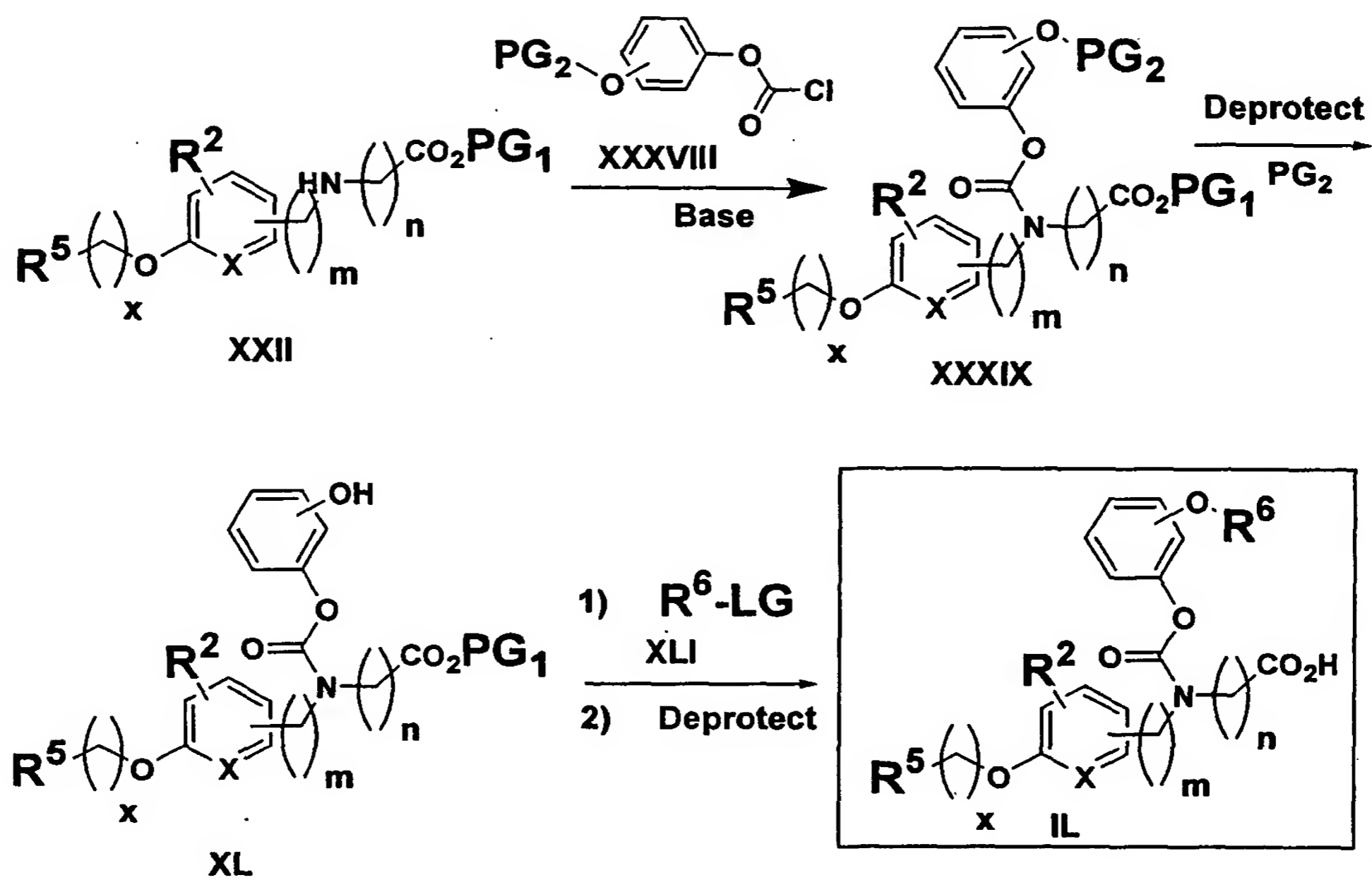


Scheme 8

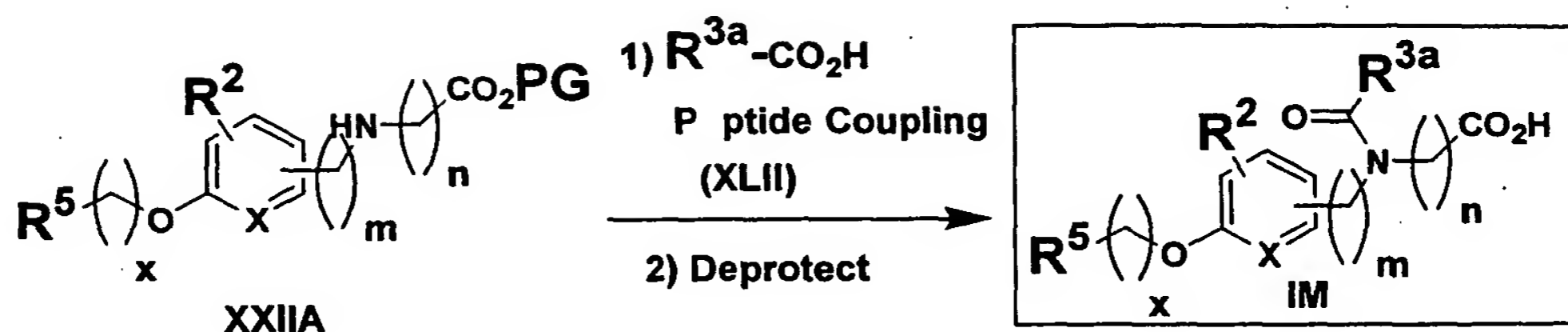




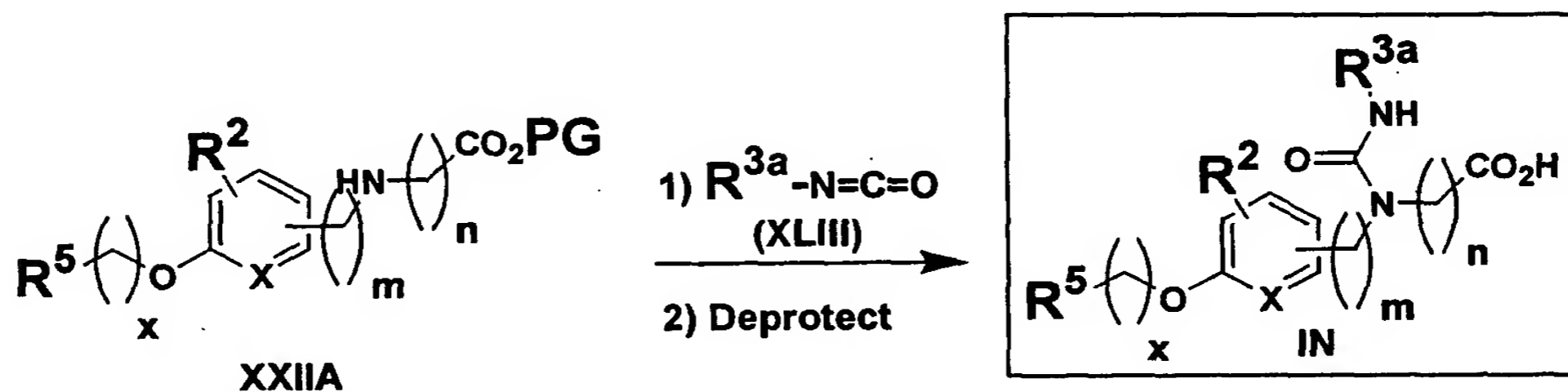




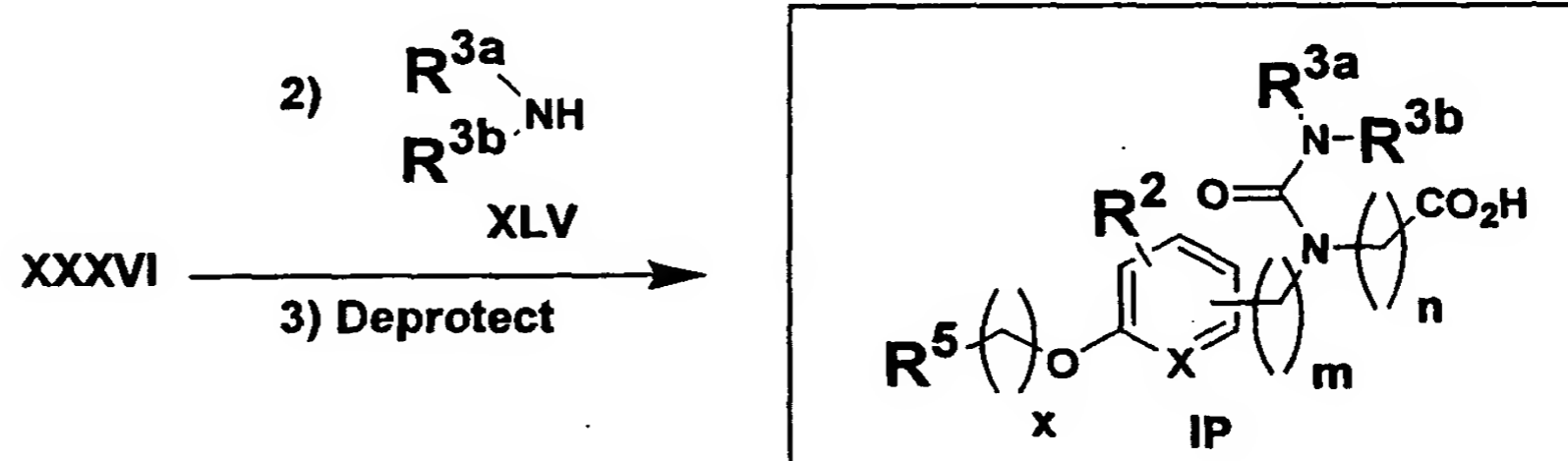
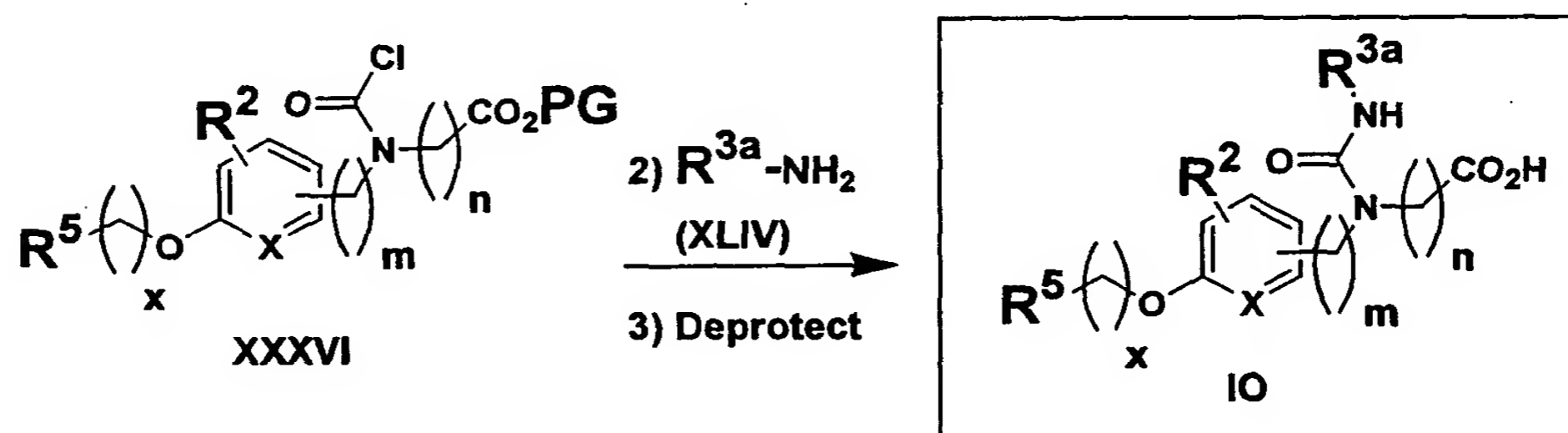
Scheme 12



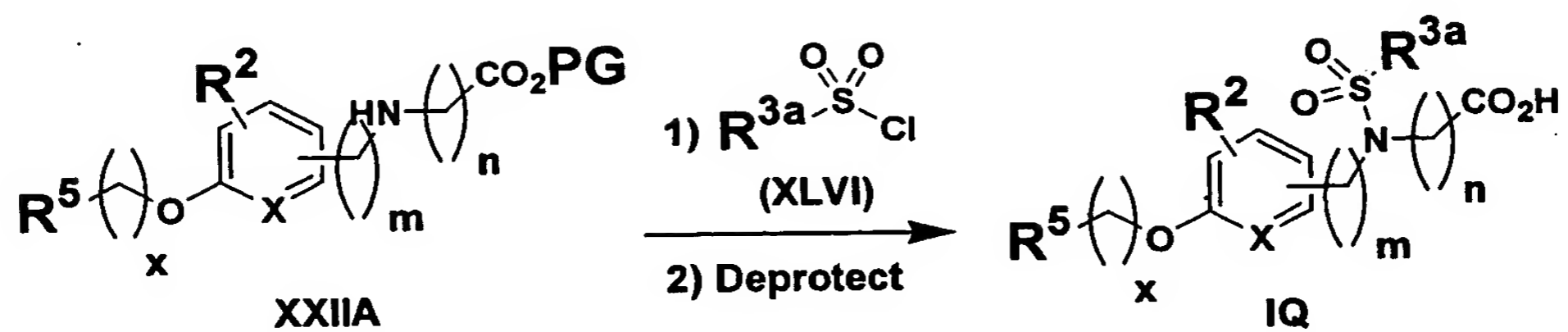
Scheme 13



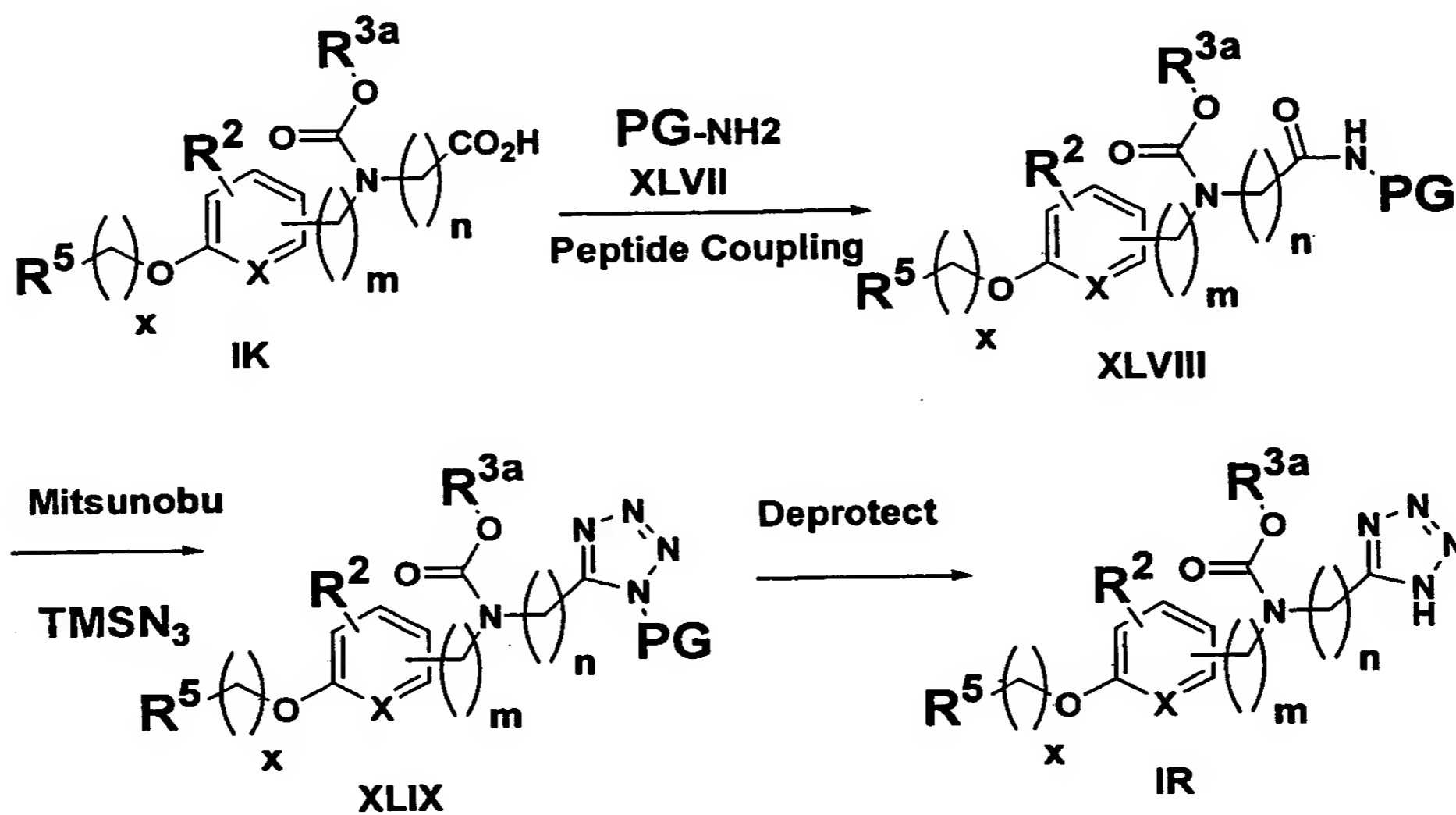
Scheme 14



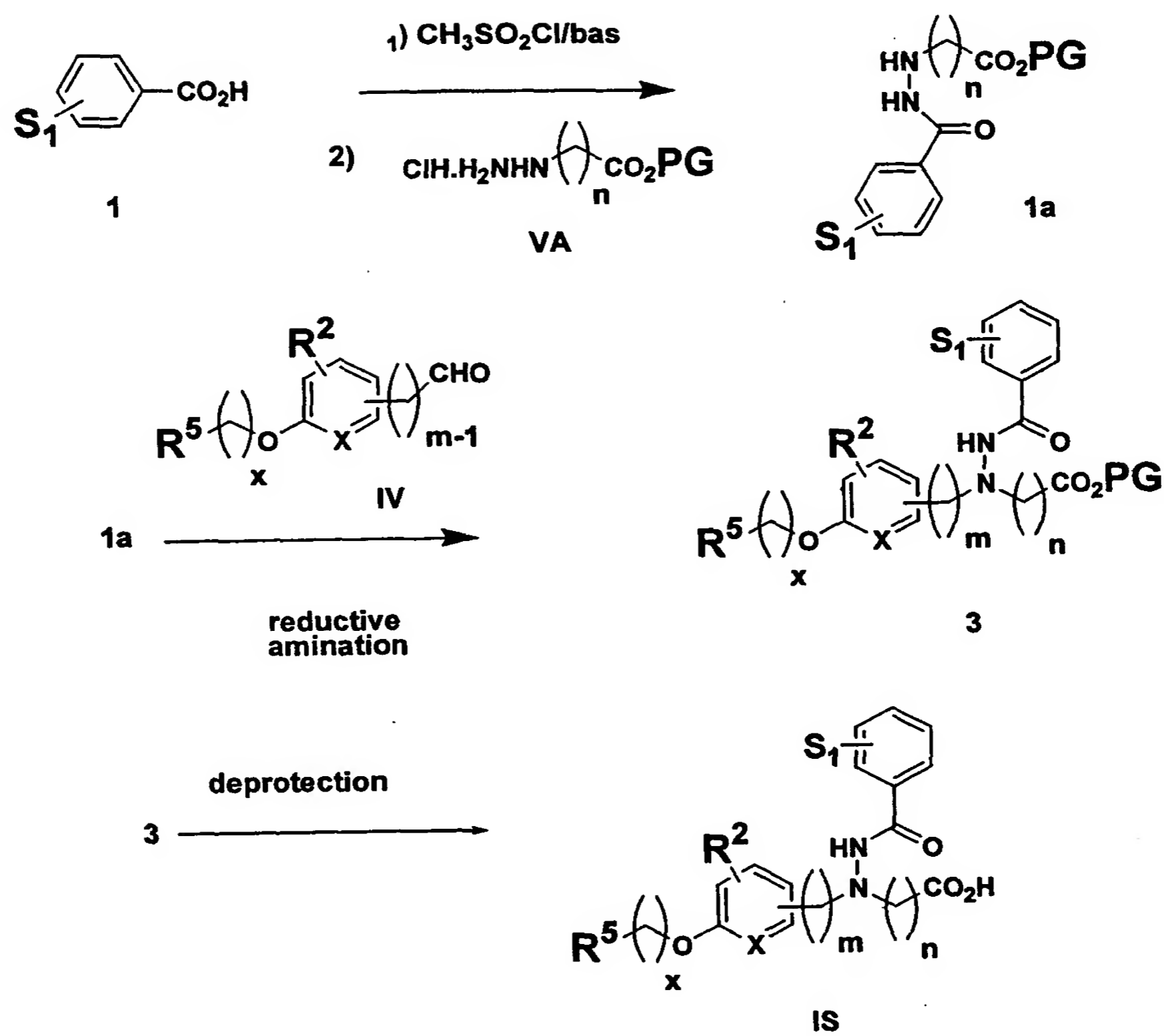
Scheme 15



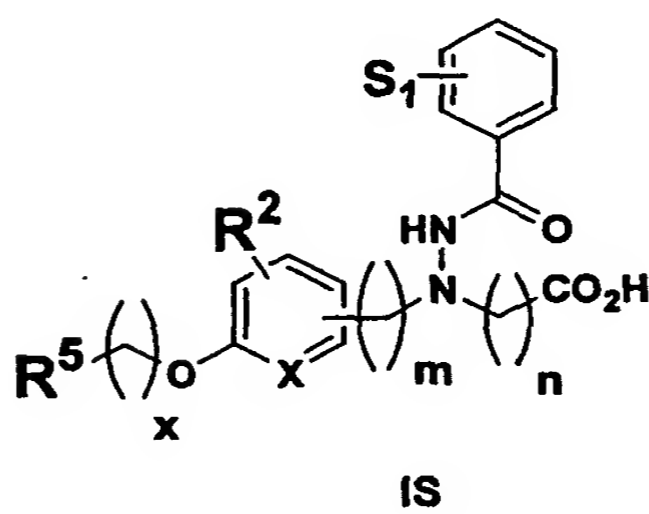
Scheme 16



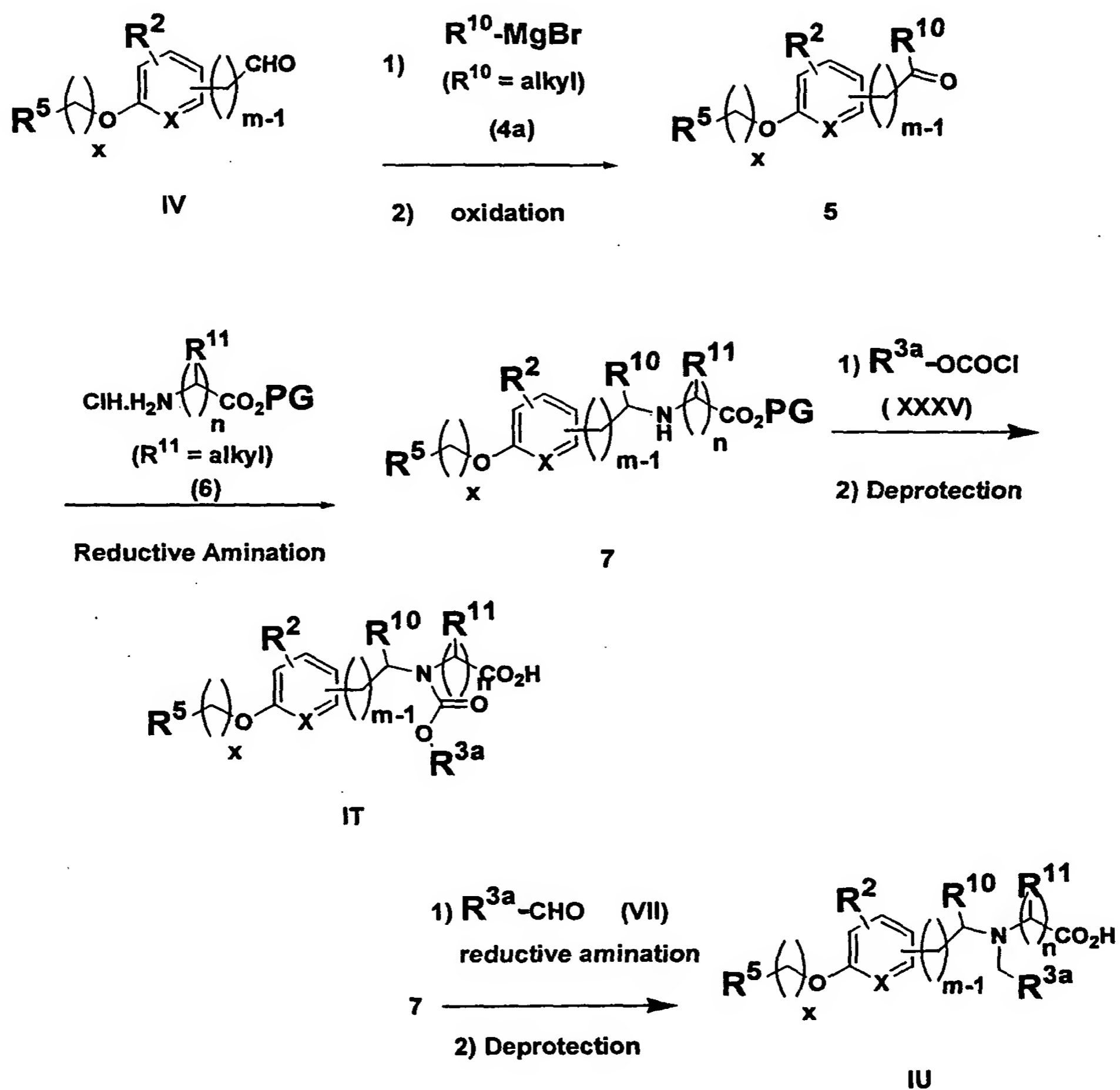
Scheme 17



Scheme 18



- 46 -

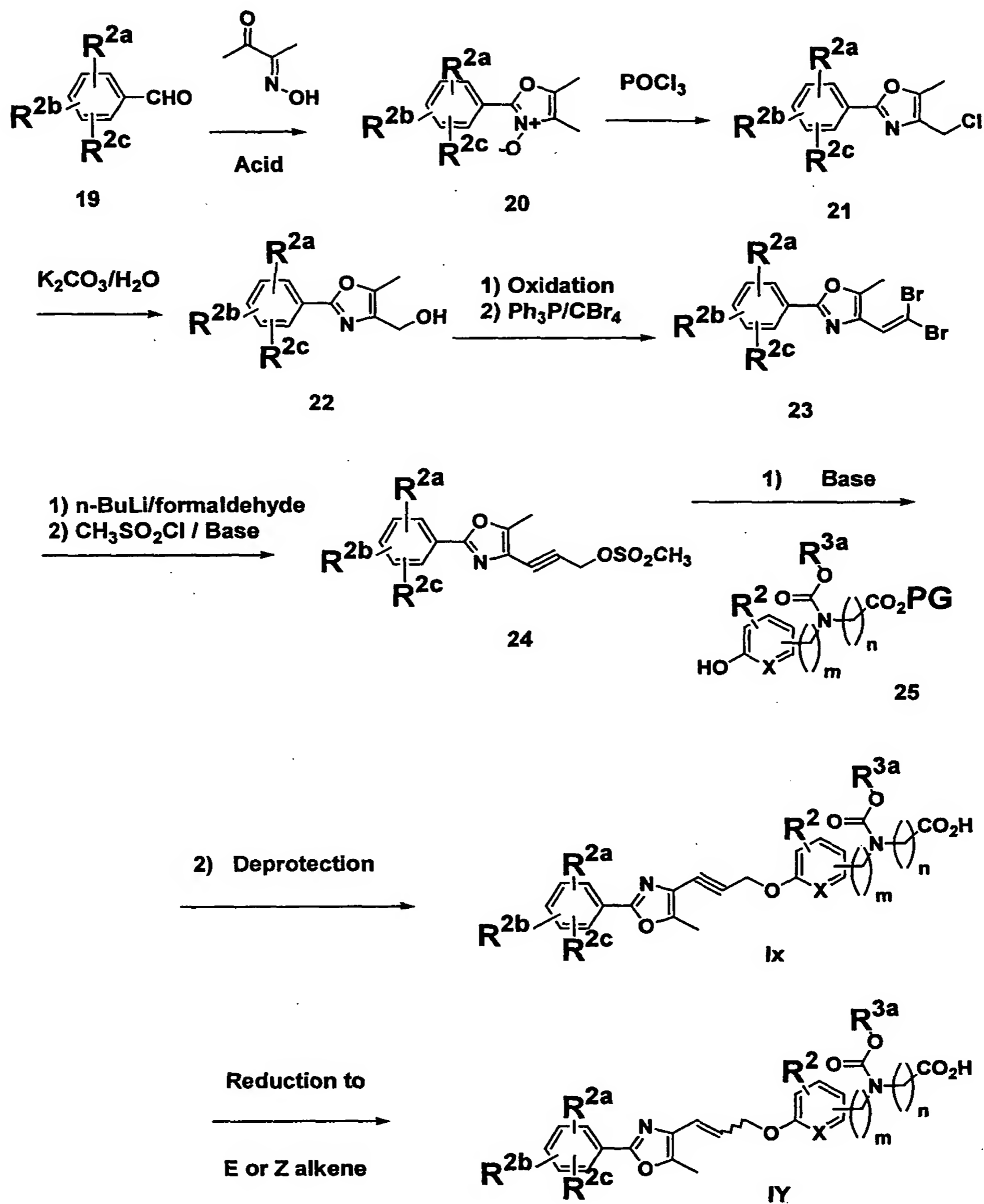


Scheme 20

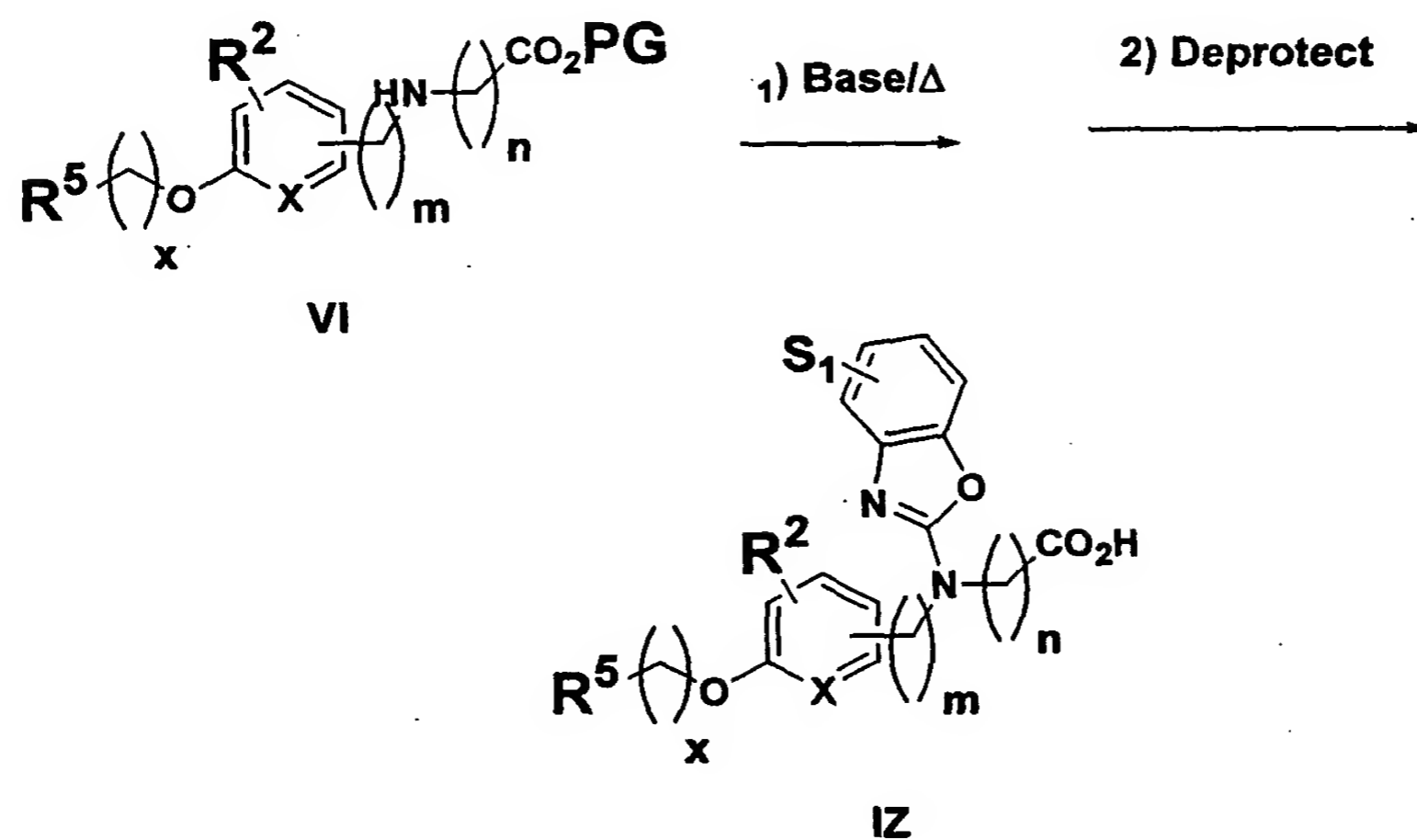
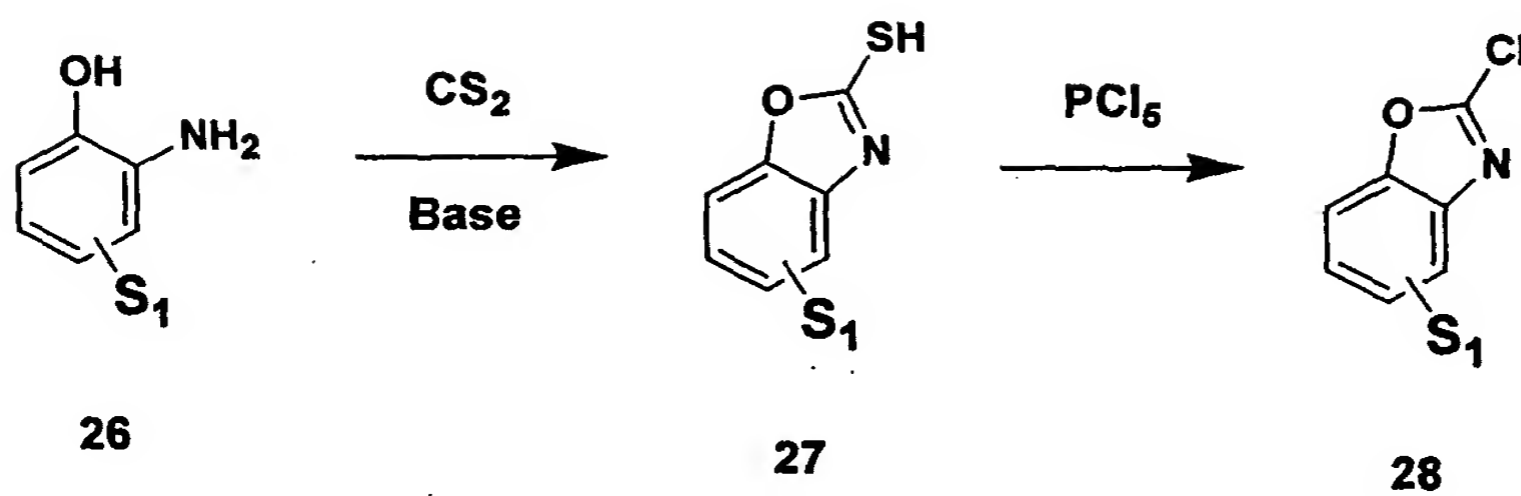




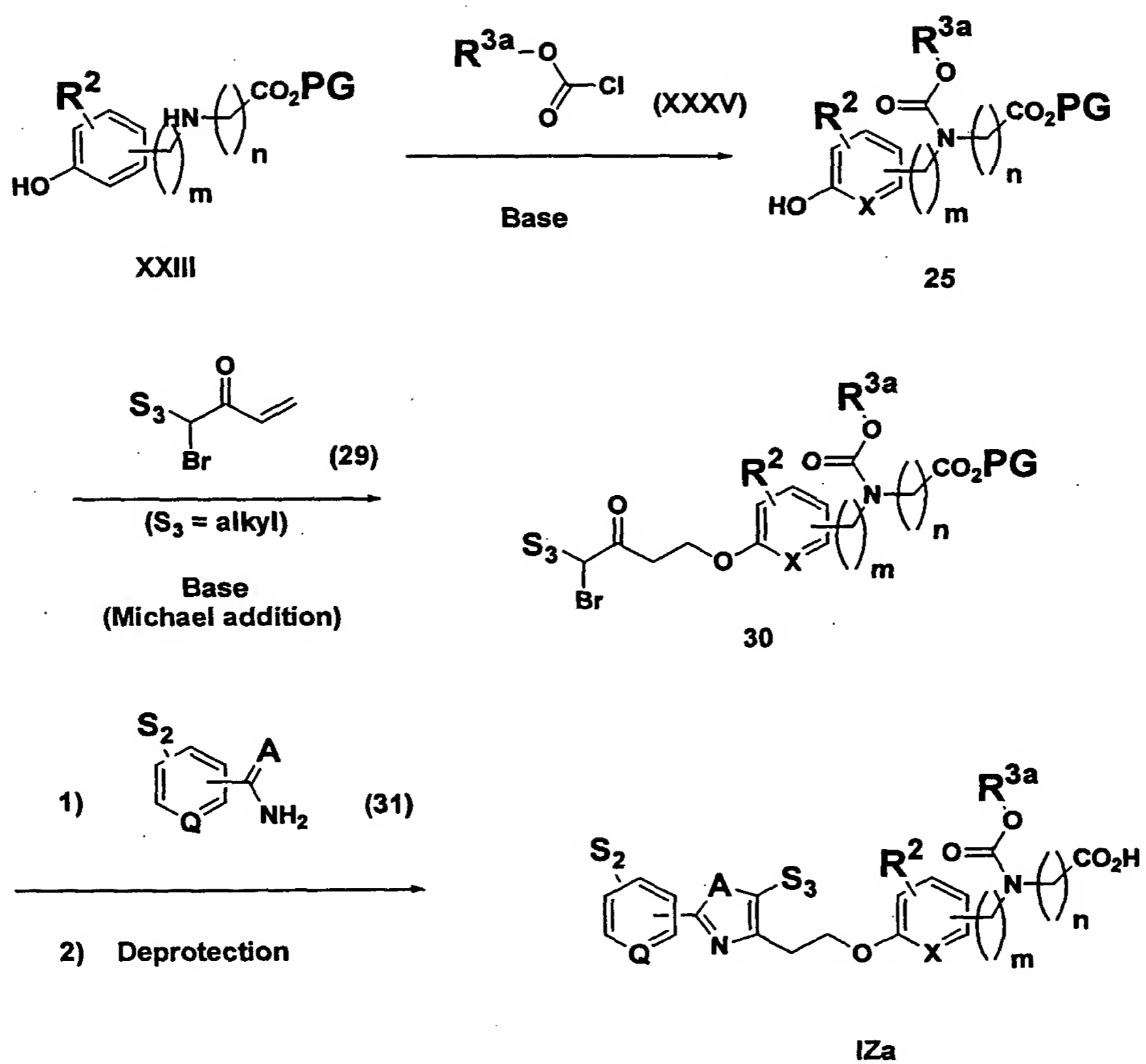




Scheme 24



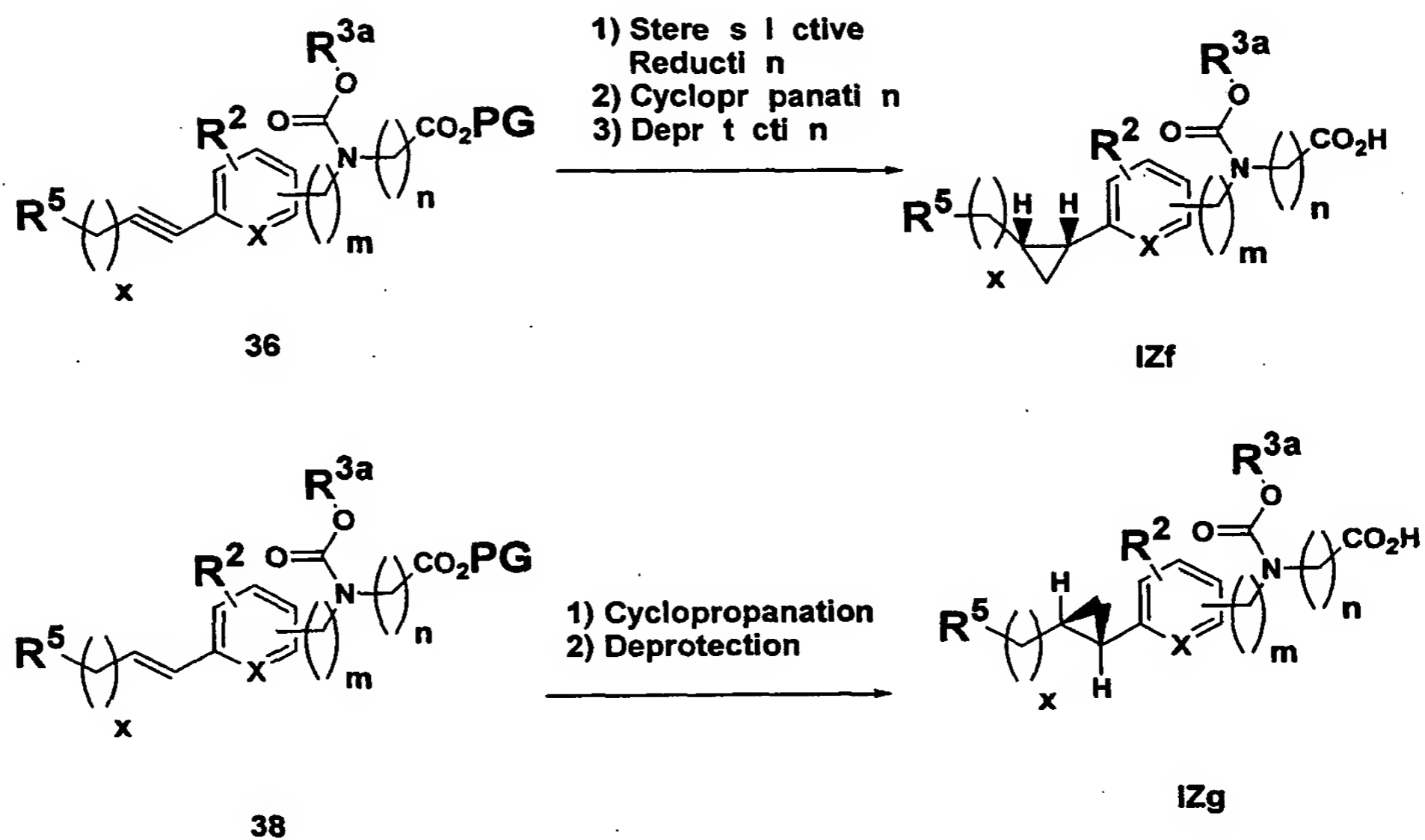
Scheme 25

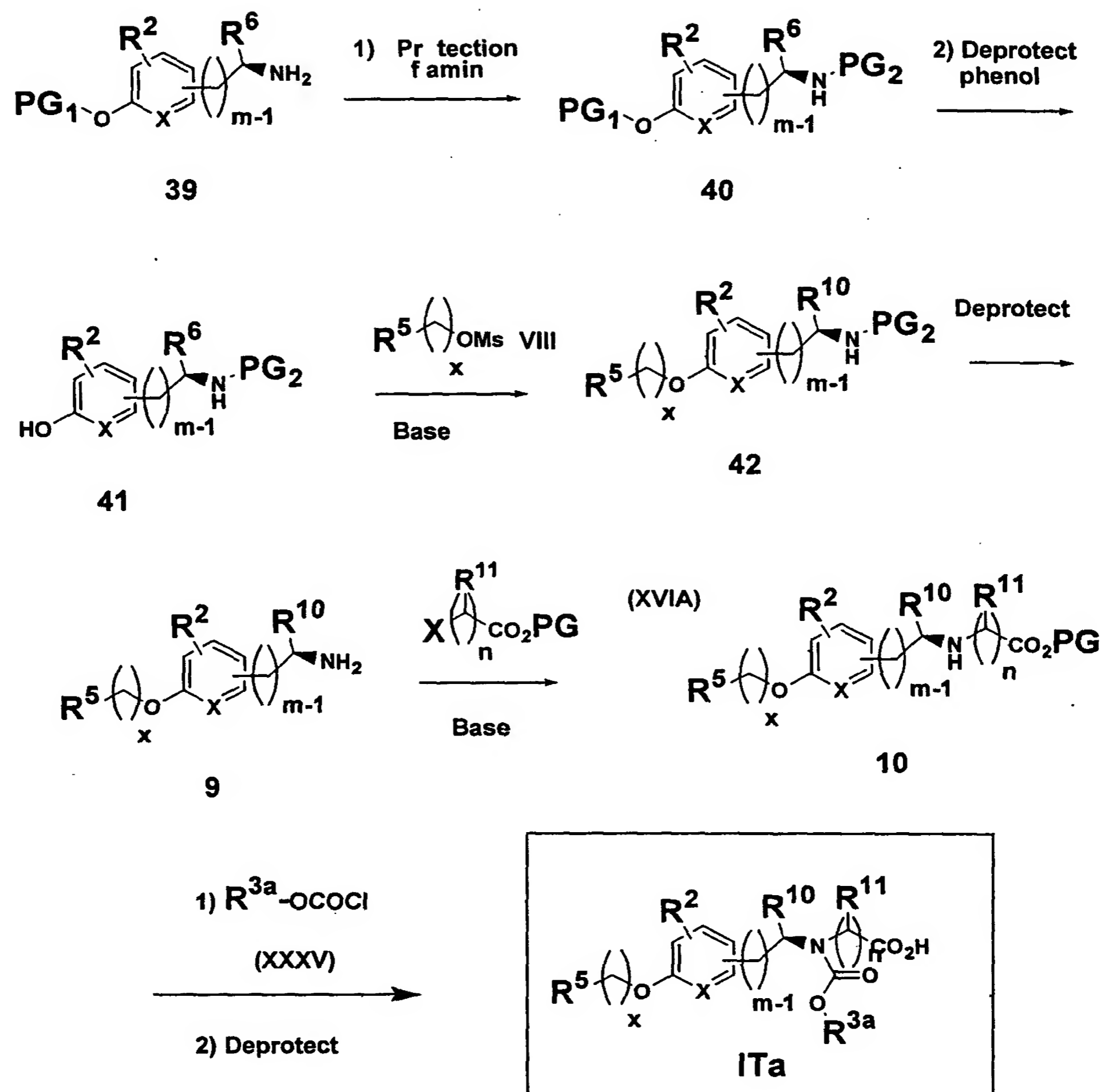


Scheme 26





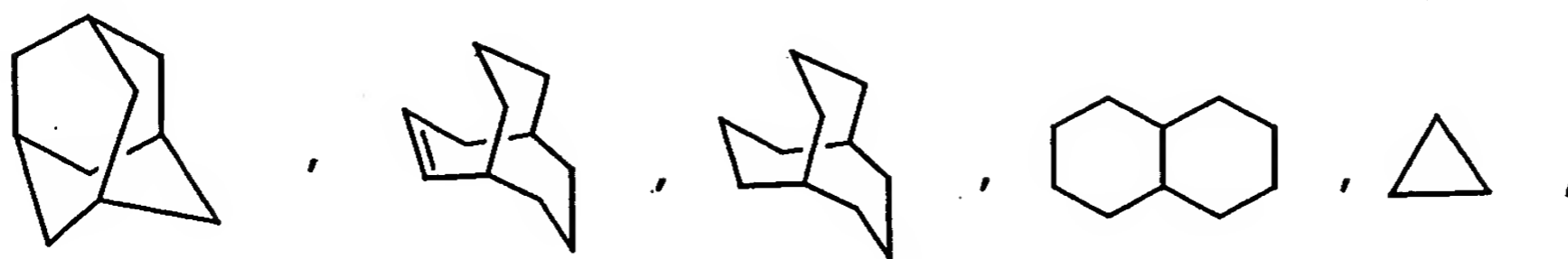




Scheme 31



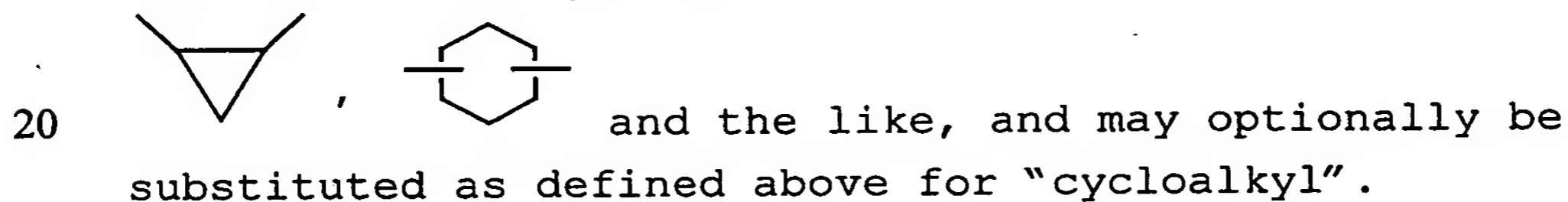
Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "cycloalkylene" as employed herein refers to a "cycloalkyl" group which includes free bonds and thus is a linking group such as



The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-

hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the substituents for alkyl set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl set out herein.

The terms "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

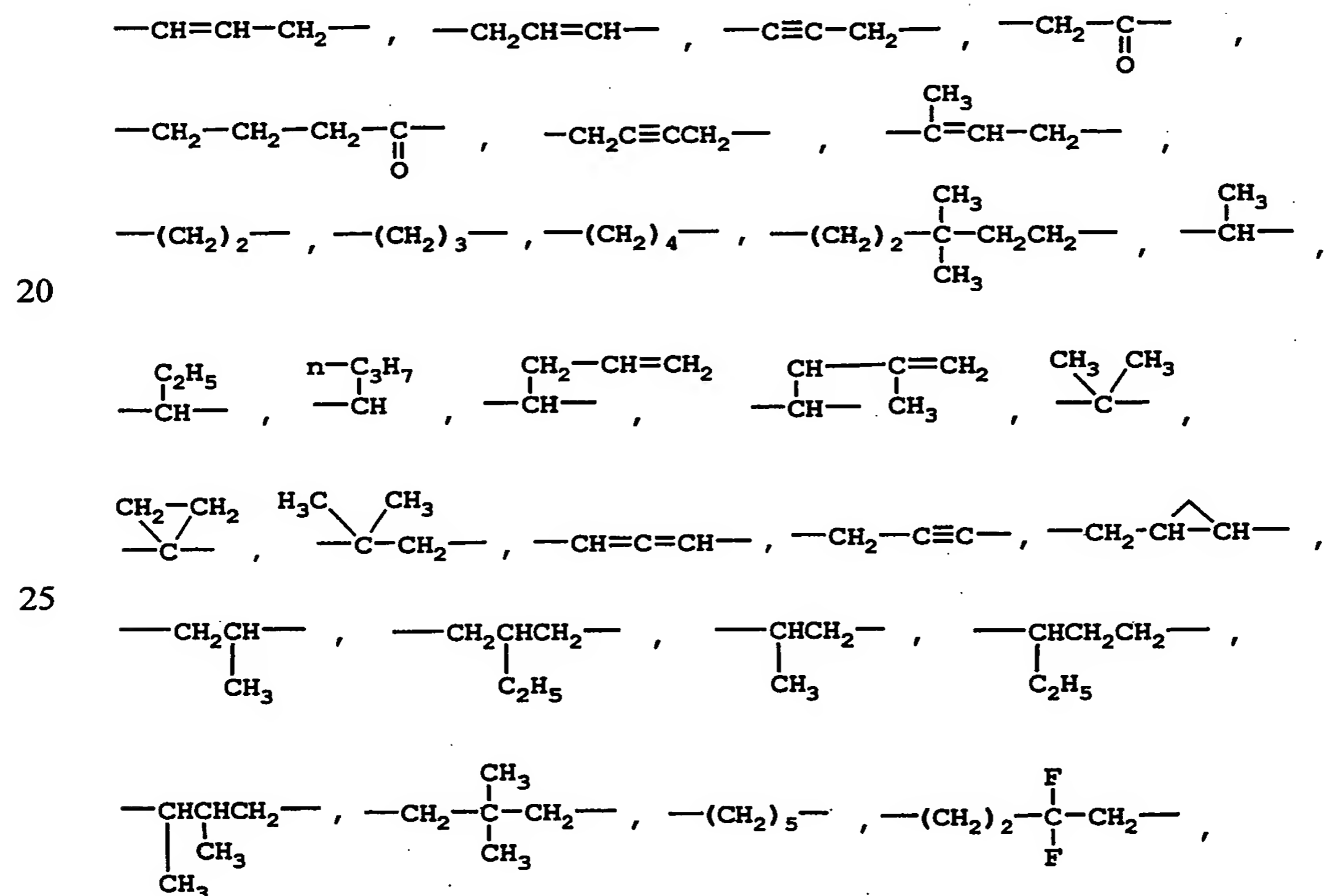
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

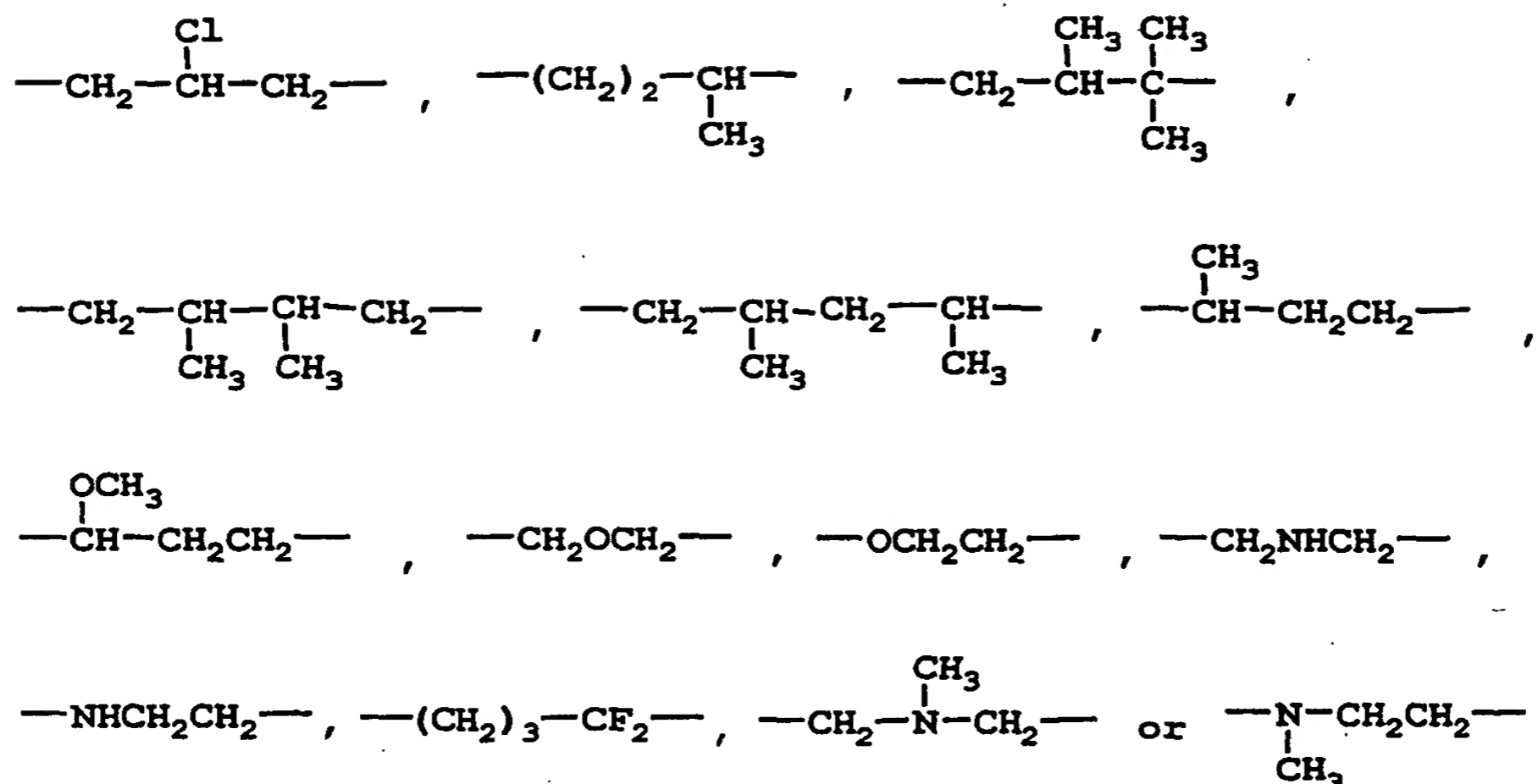
Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are

termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

- (CH₂)_x, (CH₂)_m, (CH₂)_n or (CH₂)_y includes alkylene, allenyl, alkenylene or alkynylene groups, as defined herein, each of which may optionally include an oxygen or nitrogen in the normal chain, which may optionally include 1, 2, or 3 substituents which include alkyl, alkenyl, halogen, cyano, hydroxy, alkoxy, amino, thioalkyl, keto, C₃-C₆ cycloalkyl, alkylcarbonylamino or alkylcarbonyloxy; the alkyl substituent may be an alkylene moiety of 1 to 4 carbons which may be attached to one or two carbons in the (CH₂)_x or (CH₂)_m or (CH₂)_n group to form a cycloalkyl group therewith.

- Examples of (CH₂)_x, (CH₂)_m, (CH₂)_n, (CH₂)_y, alkylene, alkenylene and alkynylene include

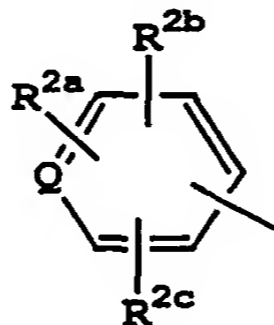




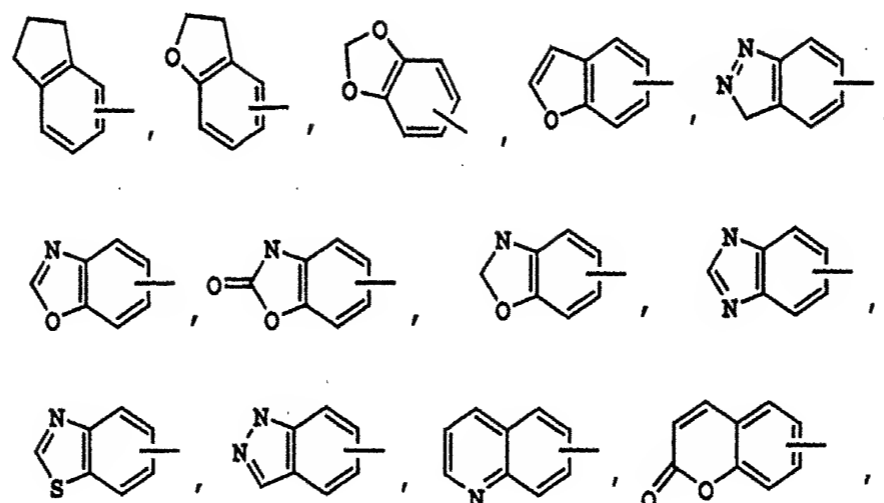
10 The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or fluorine being preferred.

15 The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" or the group



20 where Q is C, as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three
 25 additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



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and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the substituents for alkyl set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the substituents for alkyl as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

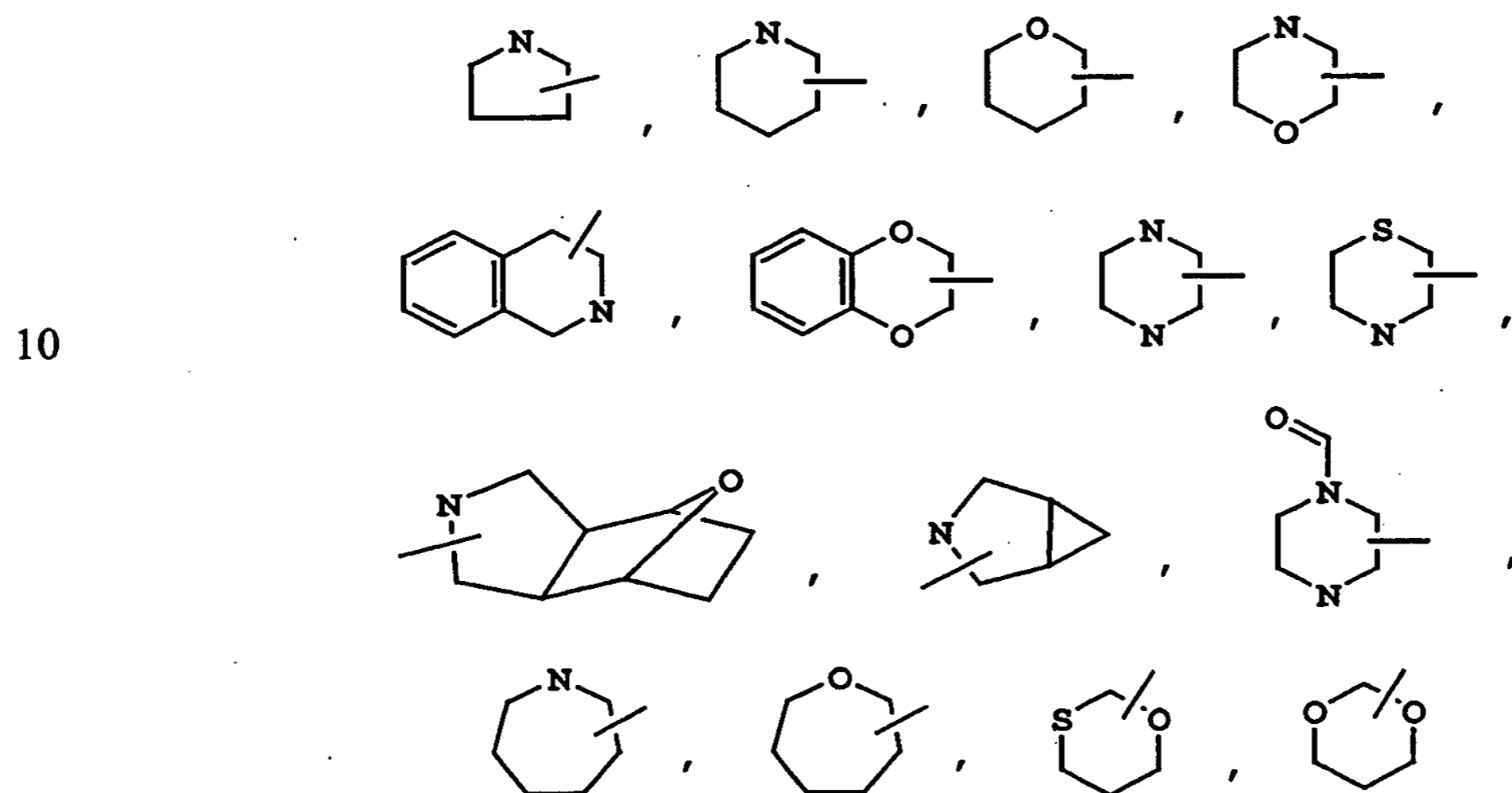
Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{smallmatrix} \text{O} \\ \parallel \\ \text{C} \end{smallmatrix} \right)$ group; examples of acyl groups include any of the R³ groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

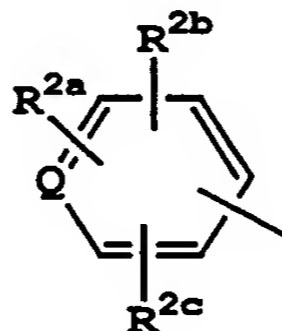
Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of

another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (where p is 1, 2 or 3), such as



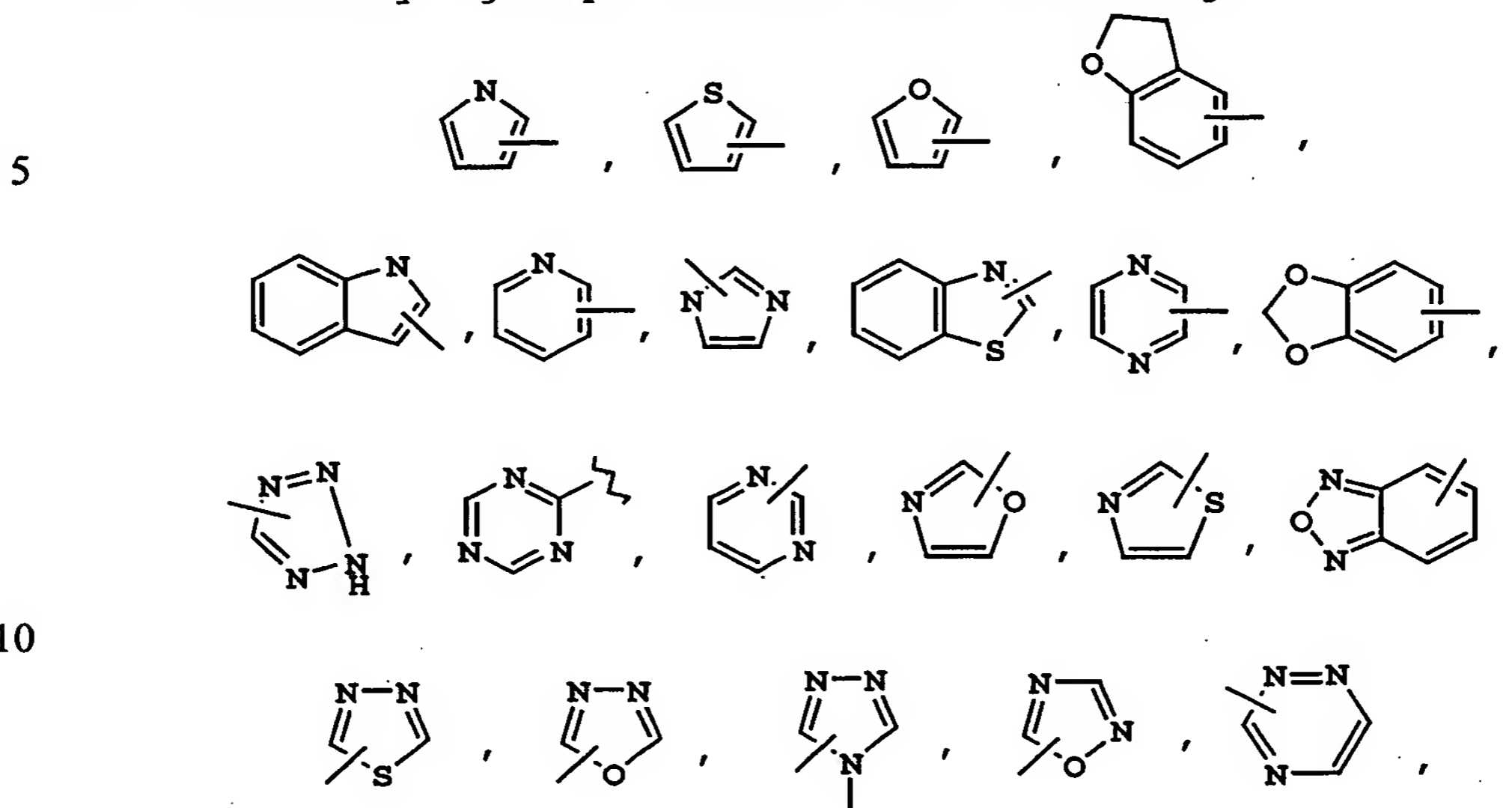
15 and the like. The above groups may include 1 to 4
substituents such as alkyl, halo, oxo and/or any of of
the substituents for alkyl or aryl set out herein. In
addition, any of the cycloheteroalkyl rings can be fused
20 to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl
ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring including



where Q is N, which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes

possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the the substituents for alkyl or aryl set out above. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

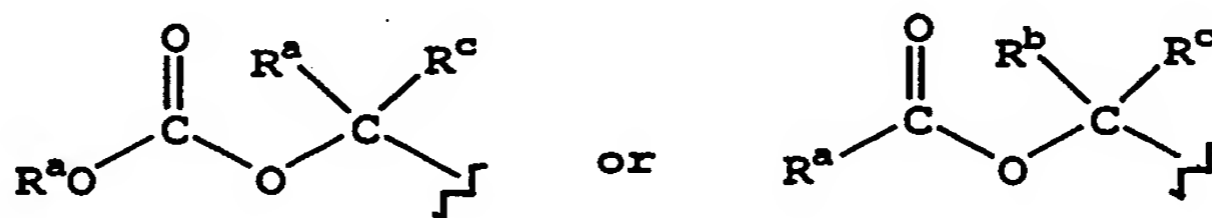
The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2 , CF_3 or $CF_3CF_2CH_2$.

The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O , CF_3O or $CF_3CF_2CH_2O$.

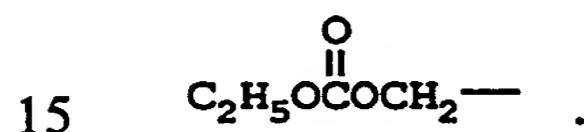
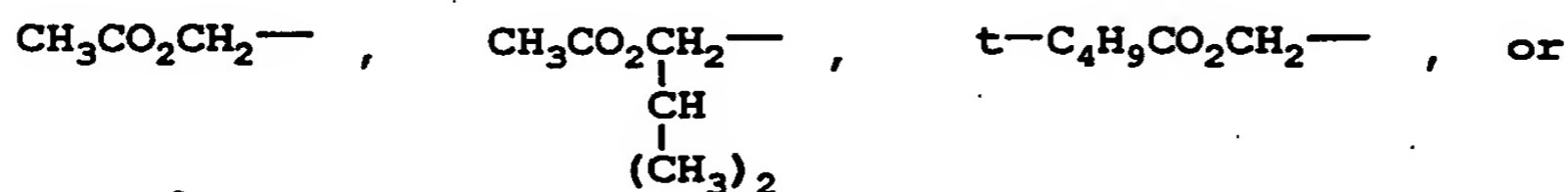
The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like. Other prodrug ester examples of R⁴ include the following groups:

(1-alkanoyloxy)alkyl such as,

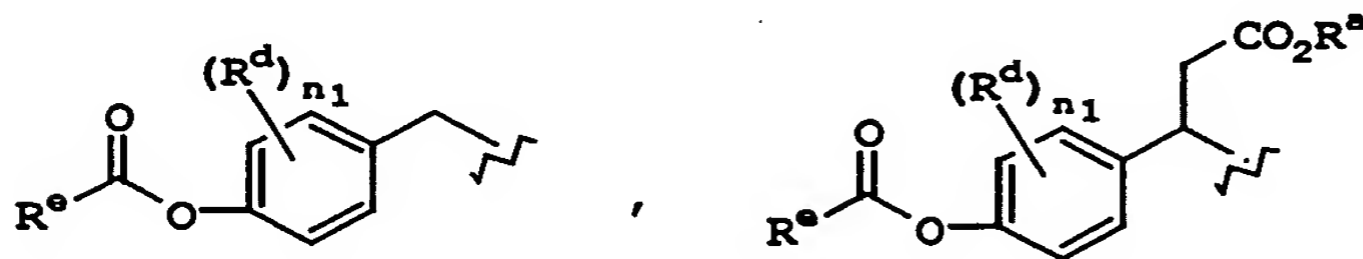
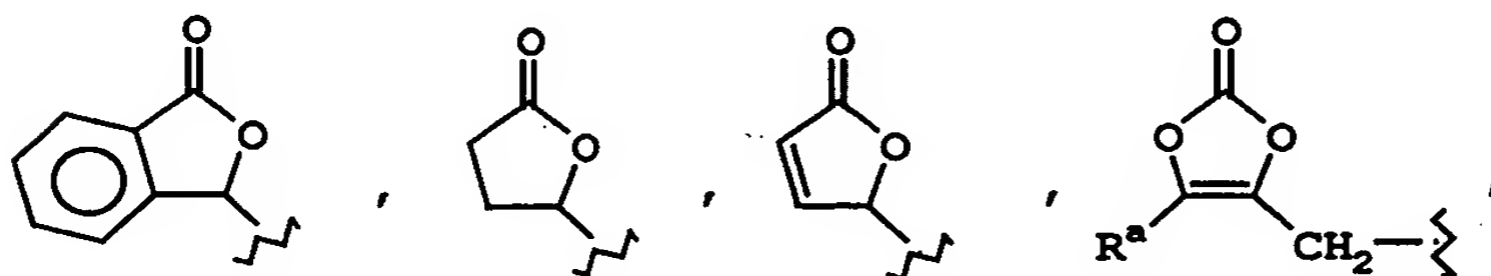


10 wherein R^a , R^b and R^c are H, alkyl, aryl or arylalkyl;
however, R^aO cannot be HO.

Examples of such prodrug esters R⁴ include



Other examples of suitable prodrug esters R⁴ include



wherein R^a can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^d is H, alkyl, halogen or alkoxy, R^e is alkyl, aryl, arylalkyl or alkoxy, and n₁ is 0, 1 or 2.

Where the compounds of structure I are in acid form they may form a pharmaceutically acceptable salt

such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, lysine (D or L), ethylenediamine, t-butylamine, t-octylamine, tris-(hydroxymethyl)aminomethane (TRIS), N-methyl glucosamine (NMG), triethanolamine and dehydroabietylamine.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Where desired, the compounds of structure I may be used in combination with one or more hypolipidemic agents or lipid-lowering agents and/or one or more other types of therapeutic agents including antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, and/or anti-osteoporosis agents, which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The hypolipidemic agent or lipid-lowering agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxxygenase inhibitors, cholesterol absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile

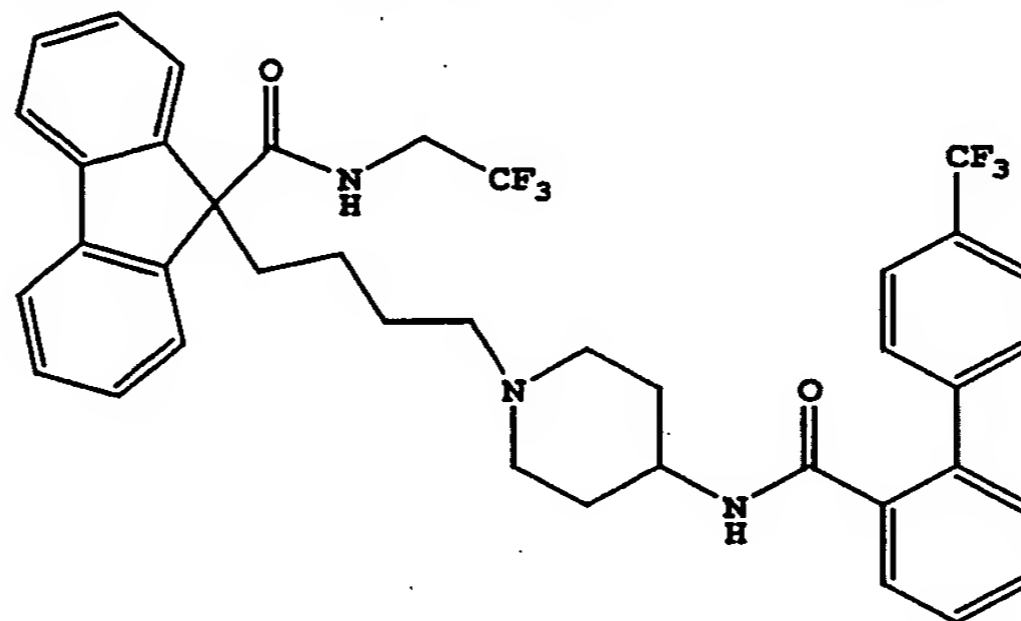


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All of the above U.S. Patents and applications are incorporated herein by reference.

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The squalene synthetase inhibitors suitable for
35 use herein include, but are not limited to, α -phosphono-
sulfonates disclosed in U.S. Patent No. 5,712,396, those
disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31,

No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in

U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

- 5 The hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, 10 Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, 15 Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfanyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, 20 Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, 25 Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. 30 Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

- 35 The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

5 The hypolipidemic agent may be an ileal Na^+ /bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

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cerivastatin, itavastatin and visastatin and ZD-4522.

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applications discussed above.

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compounds of structure I will be employed in a weight

ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as
5 glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β -cells, with glyburide and glipizide being preferred,
10 which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to
15 about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the
20 same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

25 The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin[®], disclosed in U.S. Patent No.
30 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer,
35 isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or



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Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are
5 incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin
10 Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998).

15 The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. provisional application No. 60/158,773, filed October 12, 1999 (attorney file LA49), employing dosages as set out therein. Preferred are the compounds designated as preferred in the above
20 application.

The antidiabetic agent may be an $\alpha P2$ inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5,
25 1999 (attorney file LA27*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be a DP4 inhibitor such as disclosed in Provisional Application 60/188,555 filed
30 March 10, 2000 (attorney file LA50), WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as
35 disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et

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5 GB98/284425 (KaroBio), and U.S. Provisional Application
60/183,223 filed February 17, 2000, with compounds of the
KaroBio applications and the above U.S. provisional
application being preferred.

10 employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

15 formula I or in different dosage forms, in dosages and
regimens as generally known in the art or in the PDR.

20 antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β -adrenergic blockers and other types of antihypertensive agents including diuretics.

25 mercapto (-S-) moiety such as substituted proline
derivatives, such as any of those disclosed in U.S. Pat.
No. 4,046,889 to Ondetti et al mentioned above, with
captopril, that is, 1-[(2S)-3-mercapto-2-
methylpropionyl]-L-proline, being preferred, and
30 mercaptoacyl derivatives of substituted prolines such as
any of those disclosed in U.S. Pat. No. 4,316,906 with
zofenopril being preferred.

35 (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol.
Physiol. 10:131 (1983); as well as pivopril and YS980.

Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred, phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamidates disclosed in U.S. Pat. No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck), indalaprill (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983), spirapril (Schering)

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5 'more preferably from about 10 to about 150 mg.

10 mg/kg to about 1 mg/kg.

conventional carriers.

15 It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist as well as other antihypertensives disclosed herein will be as set out in the latest edition of the Physician's Desk Reference (PDR) .

Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®) amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, nadolol, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol, and clonidine HCl (Catapres®).

Diuretics which may be employed in combination with compounds of formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and indapamide.

30 Antiplatlet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

35 The antiplatelet drugs may be employed in amounts
as indicated in the PDR. Ifetroban may be employed in
amounts as set out in U.S. Patent No. 5,100,889.

Antiosteoporosis agents suitable for use herein in combination with the compounds of formula I of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax®). Dosages employed will be as set out in the PDR.

In carrying out the method of the invention, a pharmaceutical composition will be employed containing the compounds of structure I, with or without another therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 50 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

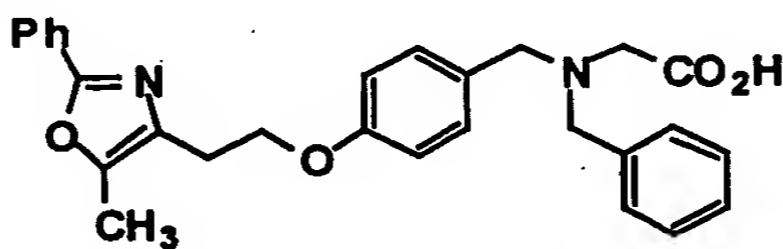
A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

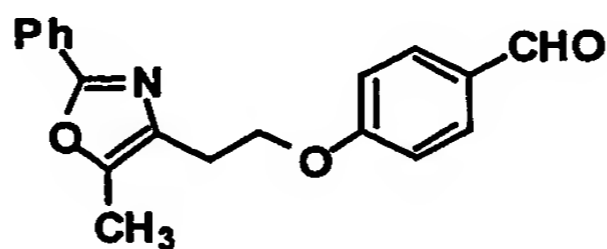
The following Examples represent preferred embodiments of the invention.

- 86 -

- BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate
 NaN(TMS)₂ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide
 5 Ph₃P = triphenylphosphine
 Pd(OAc)₂ = Palladium acetate
 (Ph₃P)₄Pd⁰ = tetrakis triphenylphosphine palladium
 DEAD = diethyl azodicarboxylate
 DIAD = diisopropyl azodicarboxylate
 10 Cbz-Cl = benzyl chloroformate
 CAN = ceric ammonium nitrate
 SAX = Strong Anion Exchanger
 SCX = Strong Cation Exchanger
 Ar = argon
 15 N₂ = nitrogen
 min = minute(s)
 h or hr = hour(s)
 L = liter
 mL = milliliter
 20 μL = microliter
 g = gram(s)
 mg = milligram(s)
 mol = moles
 mmol = millimole(s)
 25 meq = milliequivalent
 RT = room temperature
 sat or sat'd = saturated
 aq. = aqueous
 TLC = thin layer chromatography
 30 HPLC = high performance liquid chromatography
 LC/MS = high performance liquid chromatography/mass spectrometry
 MS or Mass Spec = mass spectrometry
 NMR = nuclear magnetic resonance
 35 NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet
 mp = melting point

Example 1

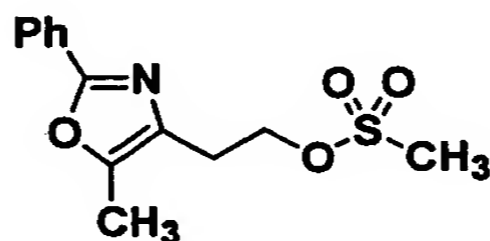
A.



To a 0°C solution of 4-hydroxybenzaldehyde (1.70 g, 12.3 mmol), 5-phenyl-2-methyl-oxazole-4-ethanol (Maybridge; 2.50 g, 14.0 mmol) and Ph₃P (4.20 g, 16.0 mmol) in dry THF (30 mL) was added dropwise DEAD (3.20 g, 15.0 mmol). The solution was stirred at 0°C for 0.5 h, then was allowed to warm to RT and stirred overnight. The orange-red solution was concentrated in vacuo and the residue was chromatographed (stepwise gradient from 5:1 to 5:2 hex:EtOAc) to give Part A compound (2.47 g, 65%) as a clear, slightly yellow viscous oil.

A1. Alternative Procedure for Preparing Part A Aldehyde

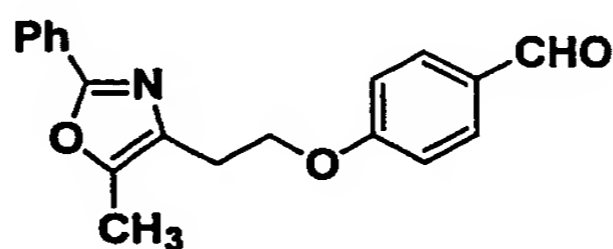
(1)



To a -5°C solution of 5-phenyl-2-methyl-oxazole-4-ethanol (20.00 g, 0.098 mol) in CH₂Cl₂ (100 mL) was added methanesulfonyl chloride (12.40 g, 0.108 mol) in one portion (exothermic reaction). After recooling to -5°C, Et₃N (11.1 g, 0.110 mol) was added slowly over 30 min (internal temperature <3°C). The reaction was allowed to warm to RT and stirred for 1 h (reaction monitored by analytical HPLC), at which point starting material had been consumed. The reaction was washed with aqueous HCl (2 x 50 mL of a 3N solution). The combined aqueous layers were extracted with CH₂Cl₂ (50 mL). The combined organic extracts were successively washed with satd. aqueous NaHCO₃ and brine (50 mL each), dried (Na₂SO₄), and concentrated to ~30 mL volume. Methyl tert-butyl ether (120 mL) was added and the mixture was stirred; a white solid was formed. The mixture was cooled to -20°C for

complete crystallization. The product was filtered and vacuum-dried to give the product mesylate (23.3 g, 85%) as a white solid. The mother liquor was concentrated in vacuo and recrystallized from methyl tert butyl ether/heptane to give a second crop of product mesylate (3.3 g, 12%; total yield = 97%).

(2)

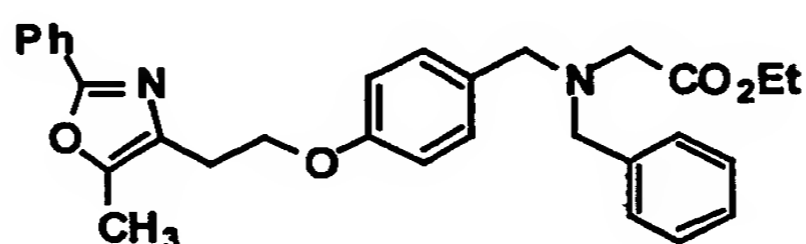


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A mixture of the above mesylate (13.6 g, 0.048 mol), 4-hydroxybenzaldehyde (7.09 g, 0.058 mol) and K_2CO_3 (9.95 g, 0.072 mol) in DMF (110 mL) was heated at 100°C for 2 h (reaction complete by analytical HPLC). The mixture was allowed to cool to RT and then poured into ice-water (400 mL) and stirred for 30 min. The solid product was filtered and washed with cold water (3 x 25 mL) and dried in vacuo at 50°-60°C overnight. The crude product was crystallized from MTBE-Hexane to give (12.2 g, 82%; 2 crops) the aldehyde (Part A1 compound) as a white solid.

20

B.



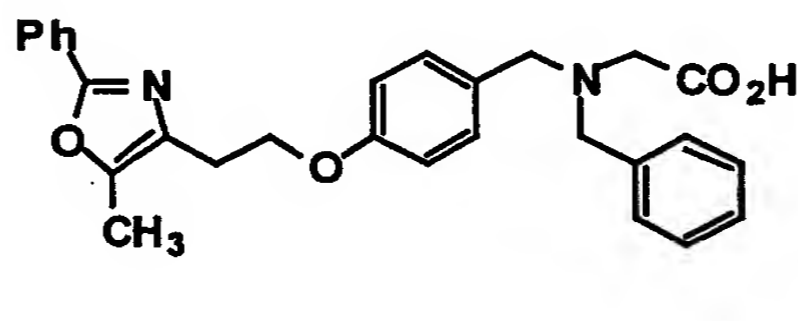
25

To a solution of N-benzyl glycine ethyl ester (43 mg; 0.22 mmol) and Part A1 compound (52 mg; 0.17 mmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (56 mg; 0.26 mmol). The reaction mixture was stirred vigorously overnight for 12 hours. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with EtOAc (3x 10 mL). The

30

combined organic extracts were washed with brine, dried
(Na_2SO_4), concentrated *in vacuo* and chromatographed
(hex:EtOAc 4:1) to give Part B compound (45 mg; 55%) as a
pale yellow oil in addition to recovered starting
5 material (14 mg; 27%).

C.

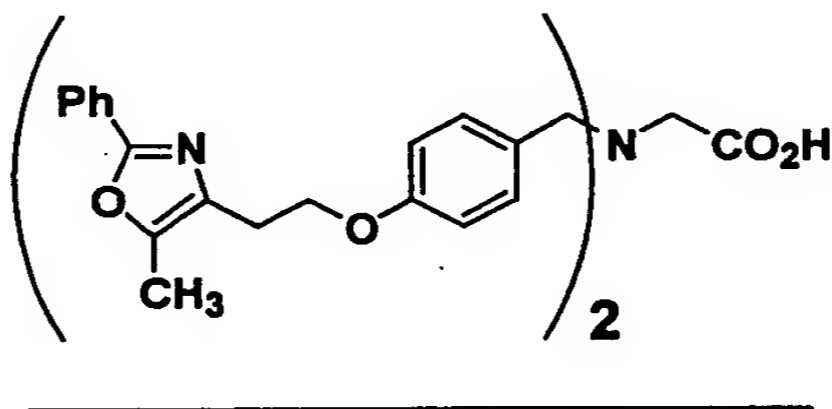


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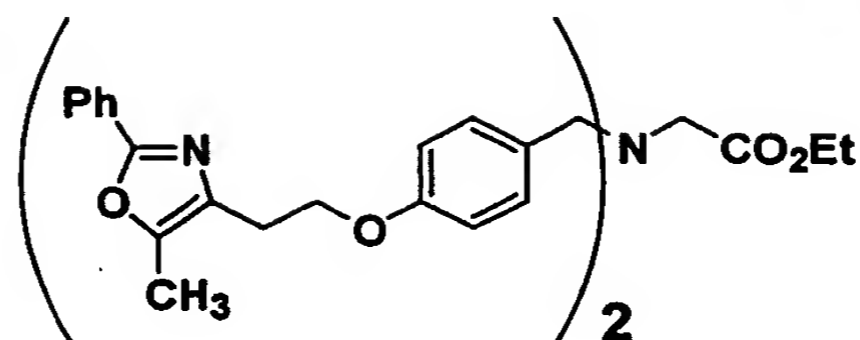
To a solution of Part B compound (45 mg) in MeOH (2
mL) was added aqueous NaOH (3 mL of a 1M solution). The
solution was stirred overnight for 14 h and then
acidified to pH 5 with excess aqueous HCl (1M solution).
15 The mixture was extracted with EtOAc (2 x 10 mL); the
combined organic extracts were washed with brine, dried
(Na_2SO_4), and concentrated *in vacuo* to give the desired
acid which was still contaminated with starting material.
This mixture was dissolved in MeOH (2 mL) and aqueous
20 NaOH (3.0 mL of a 1M solution) and the resulting solution
was refluxed for 1.5 h. Acidic extractive workup as
above gave the desired title compound as a colorless
solid (28 mg; 71%). $[\text{M} + \text{H}]^+ = 457.2$

25

Example 2

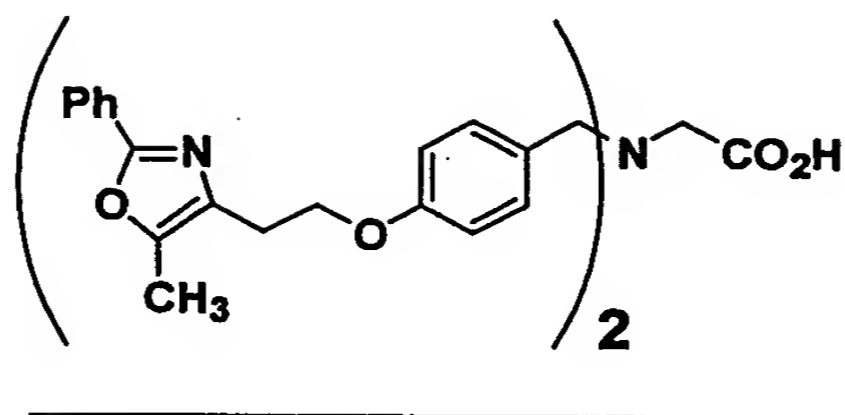


A.

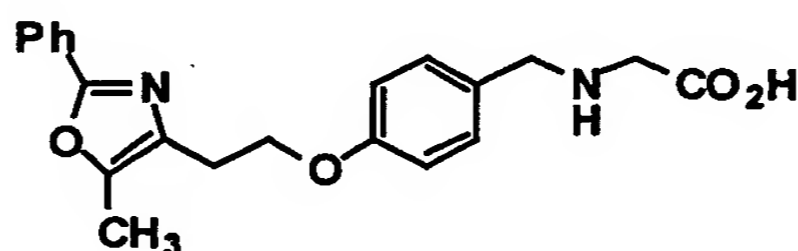


To a solution of Example 1 Part A compound (147 mg;
5 0.479 mmol) and glycine ethyl ester hydrochloride (73 mg;
0.52 mmol) in DCE (2 mL) was added Et₃N and NaBH(OAc)₃
(156 mg; 0.74 mmol) and the reaction was stirred
overnight at RT. Flash chromatography (stepwise gradient
from 7:3 to 2:3 hex: EtOAc) gave 35 mg (21%) of the
10 dibenzyl glycine ester (Example 2 Part A compound). In
addition, 127 mg (67%) of the monobenzyl glycine ester
(Example 3 Part A compound) was obtained.

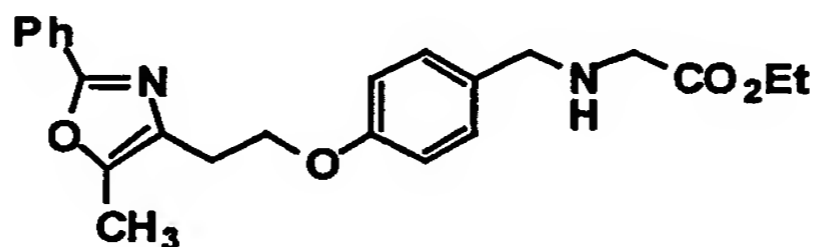
B.



5 A solution of Example 1 Part A compound (35 mg;
0.051 mmol) in MeOH (2 mL) and aqueous NaOH (3 mL of a 1M
solution) was heated under reflux for 12 h. The solution
was adjusted to pH 5 with aqueous 1M HCl and aqueous 1 M
NaOH, then extracted with EtOAc (3x). The combined
10 organic extracts were washed with brine, dried (Na₂SO₄),
and concentrated in vacuo to give title compound (13 mg)
as a colorless solid. [M + H]⁺ = 658.2

Example 3

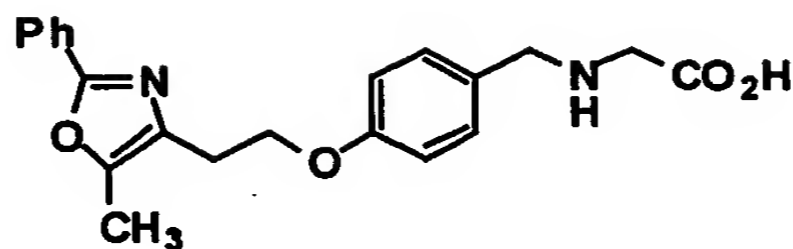
A.



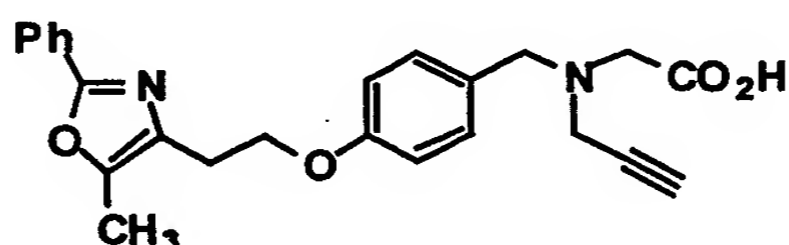
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To a solution of Example 1 Part A compound (147 mg;
0.479 mmol) and glycine ethyl ester hydrochloride (73 mg;
mmol) in DCE was added Et₃N and NaBH(OAc)₃ (156 mg; 0.74
mmol). Flash chromatography (stepwise gradient from 7:3
25 to 2:3 hex: EtOAc) gave 127 mg (67%) of the title
compound. In addition, 35 mg (21%) of the bis-benzyl
glycine ester (Example 2 Part A compound) was obtained as
a byproduct.

B.

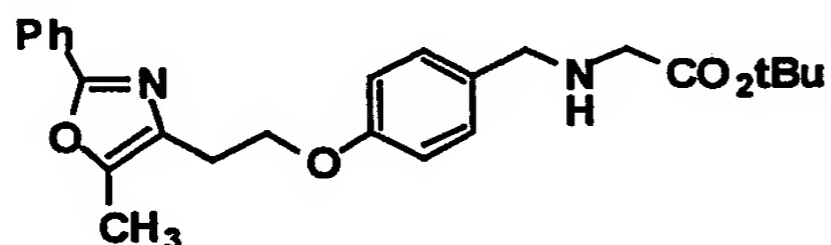


5 A solution of Part A compound (72 mg; 0.18 mmol) in aqueous NaOH (2 mL of a 1M solution) and MeOH (2 mL) was refluxed for 3 h. The reaction was adjusted to pH 5 with aqueous 1M HCl, and solids were filtered off. The filtrate was extracted with EtOAc (3x). The combined
 10 organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to give a colorless solid, which was purified by preparative HPLC (utilizing a YMC S5 ODS 20 mm x 100 mm column with a continuous gradient from 70% A:30 %B to 100% B for 10 min at a flow rate of
 15 20 mL/min, where A = 90:10:0.1 H₂O:MeOH:TFA and where B = 90:10:0.1 MeOH:H₂O:TFA) to give title compound (10 mg; 15%) as a colorless solid. [M + H]⁺ = 367.2

Example 4

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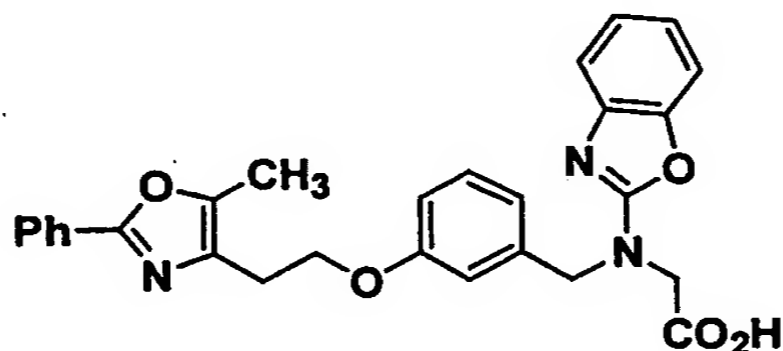
A solution of the amino t-butyl ester (0.040 g, 0.095 mmol), (prepared as described for Example 7 Part C, except that the aldehyde used in the reductive amination was Example 1 Part A instead of Example 7 Part A)



and propargyl bromide (0.014 g, 0.120 mmol) and DBU (0.5 mL; 2.96 mmol) in DCE (1 mL) was stirred at 0°C for 5 h.

TLC showed that the reaction was complete at this point. EtOAc (10 mL) was added and the organic phase was washed with H₂O and concentrated in vacuo. The residual oil was dissolved in CH₂Cl₂/TFA (1:1, 1 mL) and stirred at RT for 5 h, then concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 mm x 250 mm reverse phase column; flow rate = 25 mL/min; 30 min continuous gradient from 70:30 A:B to 100% B; where A = 90:10:0.1 H₂O:MeOH:TFA and where B = 90:10:0.1 MeOH:H₂O:TFA) to give the title compound (34 mg, 92%) as an oil. LC/MS (electrospray) gave the correct [M + H]⁺ = 405.2 for the title compound.

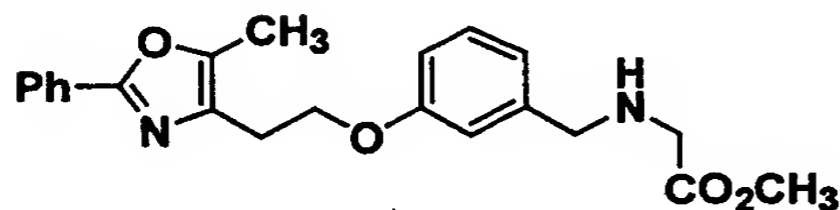
Example 5



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A solution of 2-chlorobenzoxazole (20 mg; 0.131 mmol), the secondary amine-methyl ester (52 mg; 0.146 mmol)

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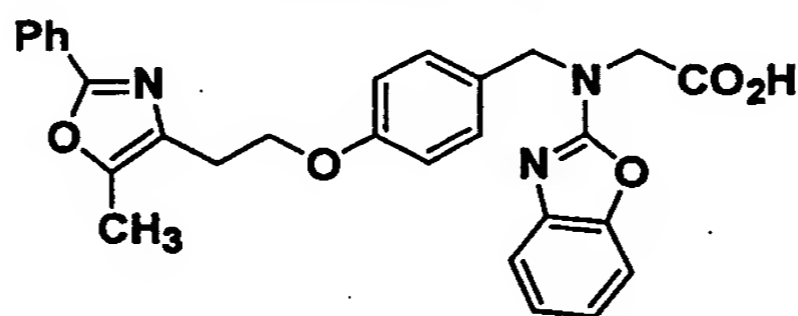


(prepared as described in Example 3 Part A except glycine ethyl ester HCl was replaced by glycine methyl ester HCl and the Example 7 Part A aldehyde was employed), and excess Et₃N (0.5 mL) in THF (2.0 mL) was heated to 100°C in a sealed tube and the reaction was monitored by LC/MS. After 4 days, starting amine had been consumed. The reaction was cooled to RT and aqueous LiOH (0.50 mL of a 1 M solution) was added to the solution. The solution was stirred at RT for 5 h, after which the hydrolysis was

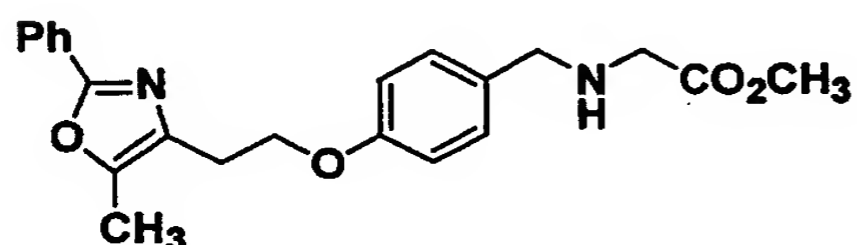
30

complete. The mixture was concentrated in vacuo to give the crude acid as an oil, which was purified by preparative HPLC (30 min continuous gradient from 70:30 A:B to 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA; flow rate = 25 mL/min; YMC S5 ODS 30 x 250 mm reverse-phase column) to give the title compound (52 mg; 82%) as a solid after lyophilization from (MeOH/H₂O). $[M + H]^+ = 484.2$

10

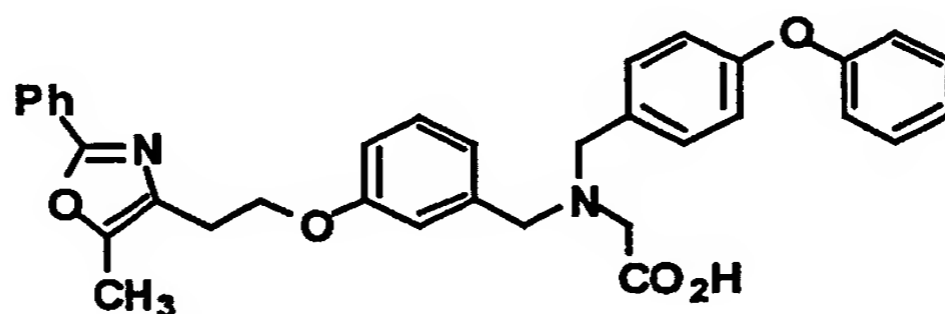
Example 6

The title compound (13 mg; 21%) was prepared in an analogous fashion to Example 5 using the corresponding secondary amine-methyl ester.



(This compound was prepared as described in Example 3 Part A except glycine ethyl ester HCl was replaced by glycine methyl ester HCl). Example 6: $[M+H]^+ = 484.2$

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Example 7



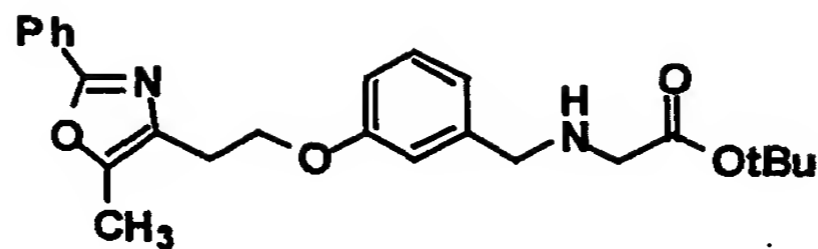
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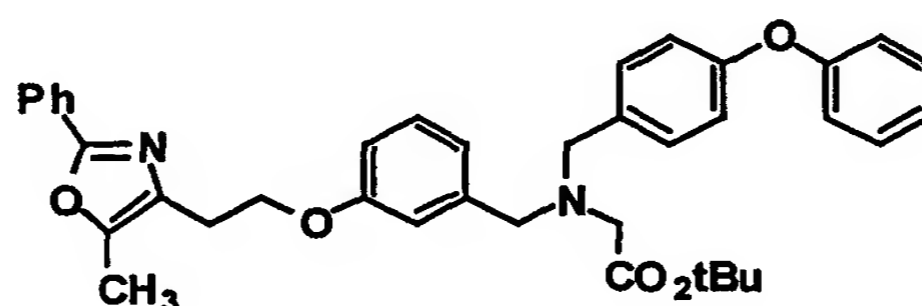
20

B.



- 5 A solution of the Part A1 compound (4.00 g; 13.0 mmol), glycine tert-butyl ester hydrochloride (2.40 g; 14.3 mmol) and Et₃N (2.18 mL; 15.7 mmol) in MeOH (30 mL) was stirred at RT for 6 h and then cooled to 0°C. A solution of NaBH₄ (594 mg; 15.7 mmol) in MeOH (10 mL) was
- 10 added portionwise at 0°C to the solution of crude imine over ~15 min. The solution was stirred at 0°C for 3 h, then at RT for 3 h, then concentrated *in vacuo* without heating to removed MeOH. The residue was partitioned between saturated aqueous NaCl and EtOAc (50 mL each).
- 15 The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow oil, which was chromatographed on SiO₂ (stepwise gradient; hex:EtOAc from 4:1 to 2:3) to give Part B compound as a pale
- 20 viscous yellow oil (4.82 g; 88%).

C.



25

- To a solution of Part B compound (0.400 g; 0.95 mmol) and 4-phenoxybenzaldehyde (0.216 g; 1.09 mmol) in DCE (5 mL) was added NaBH(OAc)₃ (0.300 g; 1.42 mmol), followed by HOAc (25 µL). The reaction was stirred at RT
- 30 for 24 h. 10% unreacted starting amine was still present by analytical HPLC. Additional aldehyde (30 mg) and

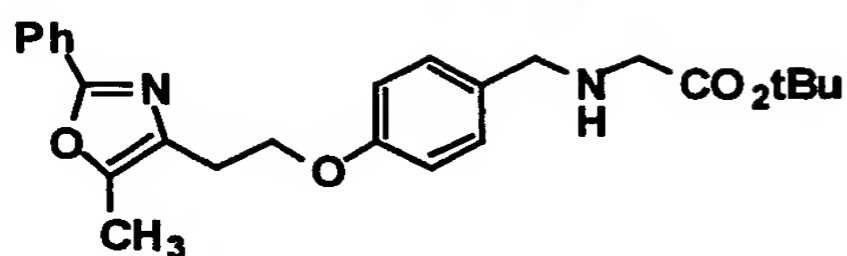
10

Cc1oc(=C(C#N1Cc2ccc(OCCCN(Cc3ccccc3)Cc4ccccc4)c5ccccc5)c6ccccc6)c7ccccc7

25

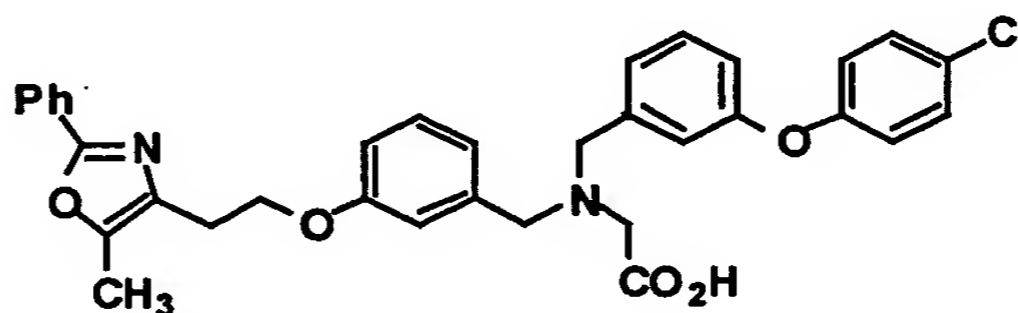
Cc1c(Cc2cc3ccccc3n2)oc(c1)c4ccccc4

30

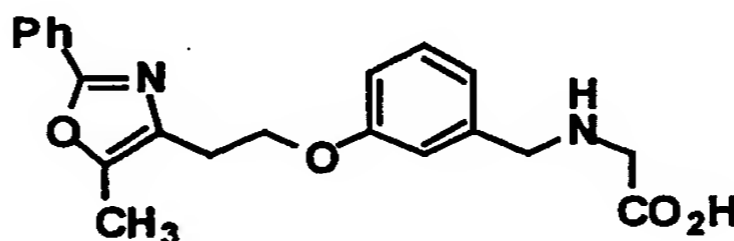


(prepared as described in Example 4),
 2-naphthaldehyde (29 mg; 0.185 mmol), and NaBH(OAc)₃ (100 mg; 0.472 mmol) in DCE (1.5 mL) was stirred at RT for 16
 5 h. TFA (1.0 mL) was then added to the mixture, which was stirred at RT for a further 12 h. Volatiles were removed in vacuo. The resulting residue was diluted with MeOH (1.5 mL), filtered, and purified by preparative HPLC (YMC S5 ODS 30mm x 250 mm column; continuous 30 min gradient @
 10 25 mL/min from 100% A to 100% B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; B = 90:10:0.1 MeOH:H₂O:TFA) to give the desired title product (39 mg; 68%) as a clear, viscous oil. [M + H]⁺ = 507.3

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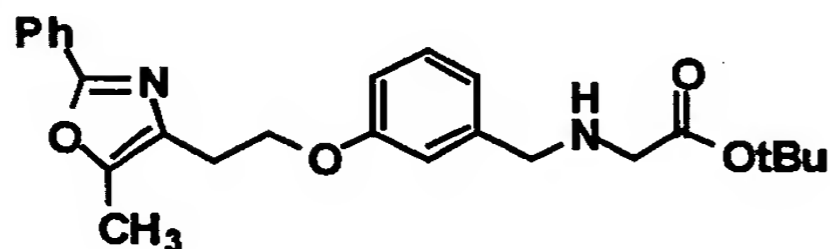
Example 9

A.



20

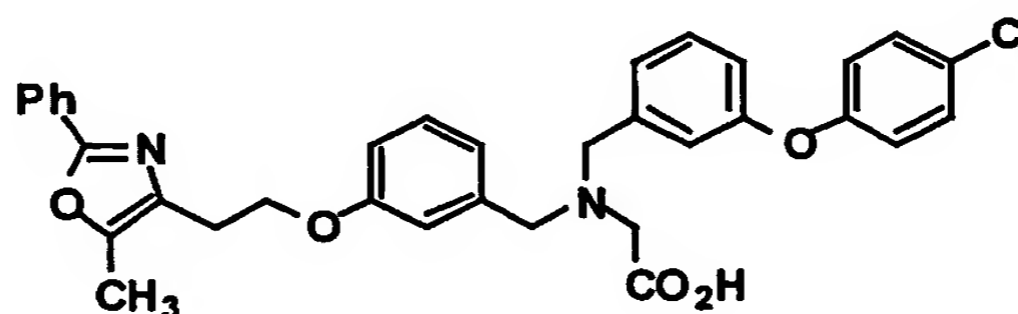
A solution of the amino acid tert-butyl ester (1.8 g, 4.27 mmol)



25 (prepared as described in Example 7 Part B), and TFA (20 mL) in CH₂Cl₂ (40 mL) was stirred at RT overnight. The solution was concentrated in vacuo, and

the residue was dissolved in CH_2Cl_2 and eluted through solid NaHCO_3 (to remove excess TFA) with excess CH_2Cl_2 . The combined filtrates were concentrated *in vacuo* to provide the desired amino acid Part A compound (1.48 g; 95%). $[\text{M} + \text{H}]^+ = 457.2$

B.



10

The title compound was prepared as part of a solution phase library run using the following exemplary procedure:

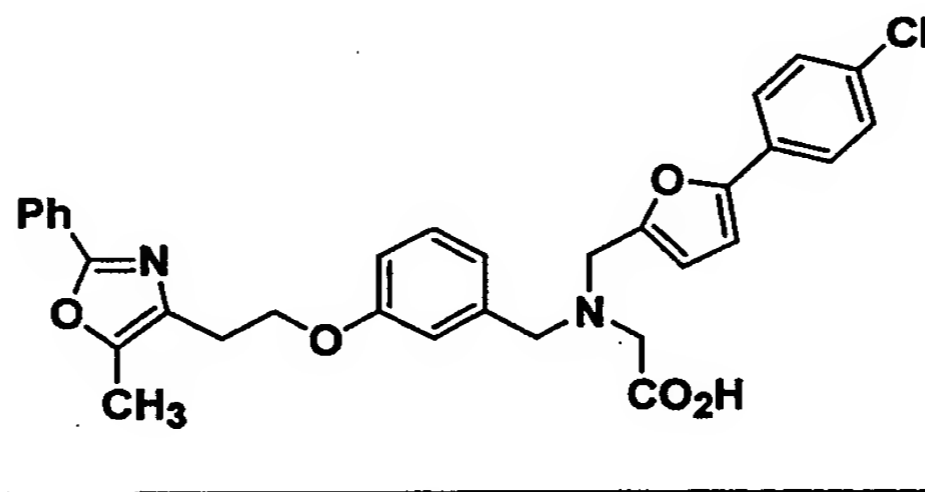
To a solution of the Part A amino acid compound (27 mg, 0.074 mmol; in 2 mL CH_2Cl_2) was added (4-chloro-phenoxy)-3-benzaldehyde (86 mg; 0.37 mmol), $\text{NaBH}(\text{OAc})_3$ (79 mg, 0.37 mmol) and HOAc (0.1 mL). The reaction was stirred at RT for 15 h.

The product was purified via solid-phase extraction using a Varian SAX cartridge (3 g of sorbent in a 6 mL column, 0.3 meq/g) by the procedure outlined below:

- 1) The column was conditioned with MeOH (10 mL) and CH_2Cl_2 (20 mL)
- 2) The reaction mixture was loaded onto the SAX column
- 3) The column was rinsed with CH_2Cl_2 (10 mL)
- 4) The column was rinsed with 1% TFA in MeOH (3 mL)
- 5) The product was eluted with 1% TFA in MeOH (20 mL)

10

(procedure used with heterocyclic aldehydes)



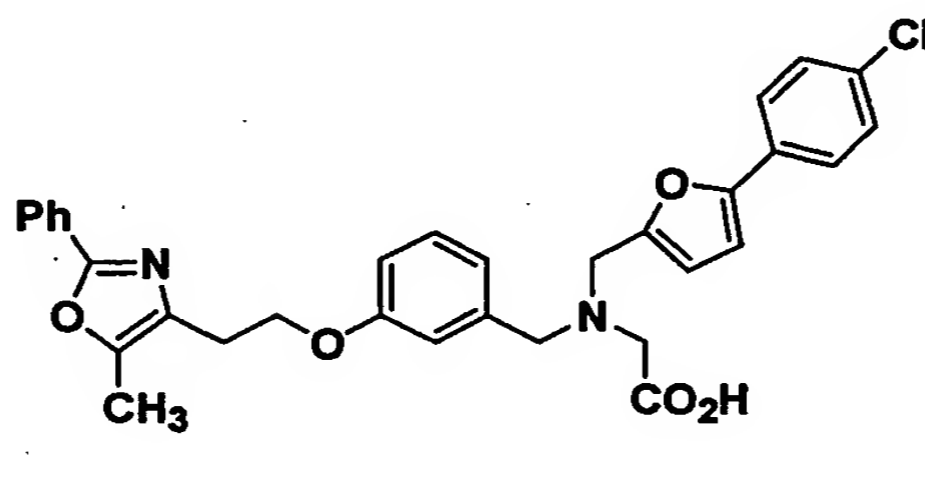
20

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)CNCC(=O)O)C

25

preparative HPLC (YMC S5 ODS 30mm x 250 mm column;
continuous 30 minute gradient @ 25 mL/min from 100% A to
100% B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; B = 90:10:0.1
MeOH:H₂O:TFA) to give the desired title product (39 mg;
5 68%) as a clear, viscous oil.

Example 10A



10

An alternative purification procedure to preparative HPLC was used as follows:

The crude reductive amination product was purified by solid-phase extraction using an SAX cartridge (United
15 Chemicals; 3 g of sorbent in a 6 mL column, 0.3 meq/g) by the procedure outlined below:

- 1) The column was conditioned with MeOH (5 mL) and CH₂Cl₂ (5 mL)
20
- 2) The reaction mixture (diluted with 2 mL CH₂Cl₂) was loaded onto the SAX column
- 3) The column was rinsed with CH₂Cl₂ (8 mL)
25
- 4) The product was eluted with 1% TFA in MeOH (20 mL)

The product-containing fractions were concentrated in vacuo using a Speed Vac for 16 h to afford the crude
30 product. This was dissolved in CH₂Cl₂:MeOH (95:5) and loaded onto a silica gel cartridge (1.5 g SiO₂) and the product was eluted with CH₂Cl₂:MeOH (95:5; 8 mL). The

5
10

10

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)CN(CCC(=O)O)Cc4ccc(Oc5ccc(F)cc5)cc4)CCC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)CN(CCC(=O)OC(C)(C)C)Cc4ccc(O)cc4)C

15

CCOC(=O)CNCCc1ccc(OCCc2c(C)c(Oc3ccccc3)n2)cc1

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25



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15

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- 30

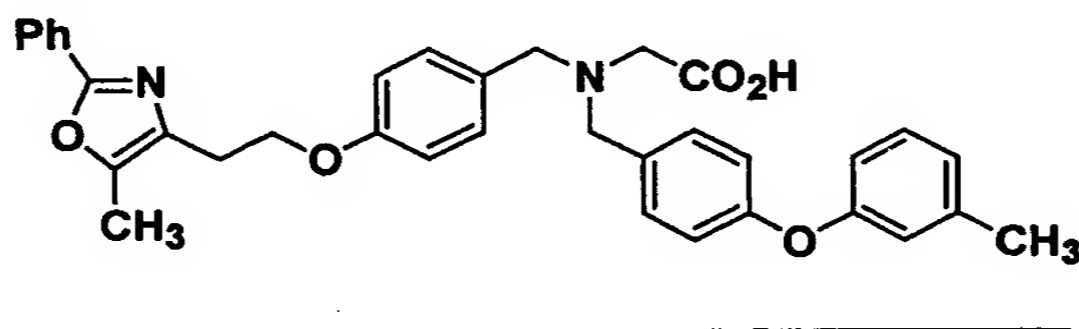
5 The product-containing fractions were concentrated
in *vacuo* to give the desired tert-butyl ester. (Some
incomplete reactions required chromatography (on SiO₂) of
the crude material to give esters of the requisite
purity). The t-butyl ester was treated with a solution
10 of 30% TFA in CH₂Cl₂ overnight. Volatiles were removed
and the residue was redissolved in CH₂Cl₂ (1 mL) and
concentrated in *vacuo* on a Speed Vac to afford the
desired title product (30 mg; 77%). Reverse phase HPLC
analysis indicated that the product purity was 90%. In
15 addition LC/MS gave the correct molecular ion [(M+H)⁺ =
567] for the desired title compound.

20

CCOC(=O)CNCCc1ccc(OCCc2c(C)c(=N)c(c2)Oc3ccccc3)cc1

- 105 -

10 B.



To a solution of the Part A boronic acid compound (40 mg, 0.072 mmol) in CH_2Cl_2 (1 mL) was added m-cresol (23 mg; 0.22 mmol) and 4A molecular sieves (150 mg; pre-dried at 400°C overnight). After stirring for 5 min, $\text{Cu}(\text{OAc})_2$ (1 eq), Et_3N (5 eq) and pyridine (5 eq) were added to the mixture. The vial was capped and air was allowed to pass into the reaction, which was stirred at RT for 24 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*.

1) The column was conditioned with MeOH (10 mL) and CH₂Cl₂ (10 mL)

- 106 -

5 4) The product was eluted with a solution of 0.5N NH_3 in MeOH.

10

15

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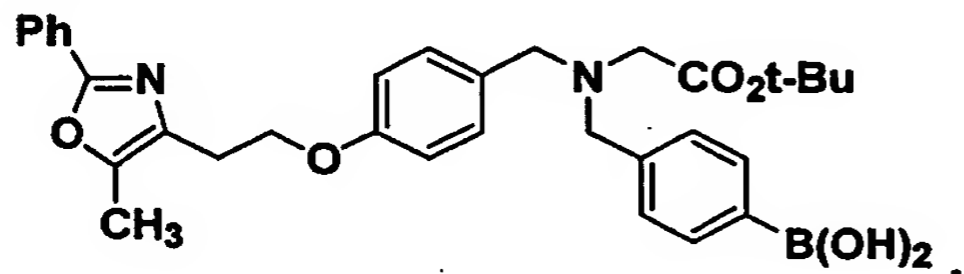
8) The product-containing fractions were collected and concentrated in vacuo to give the purified tert-butyl ester

20 The t-butyl ester was treated with a solution of 1:1
TFA in CH₂Cl₂ overnight. Volatiles were removed and the
residue was redissolved in CH₂Cl₂ (1 mL) and concentrated
in vacuo on a Speed Vac to afford the desired title
product (25 mg; 48%) as a slightly yellowish oil.
25 Reverse phase HPLC analysis indicated that the product
purity was 91%. In addition LC/MS gave the correct
molecular ion [(M+H)⁺ = 563.2] for the desired compound.

Cc1c(Cc2cc(OCc3ccc(cc3)CN(Cc4ccccc4)C(=O)O)c2)oc(c1N)c5ccccc5

30

5



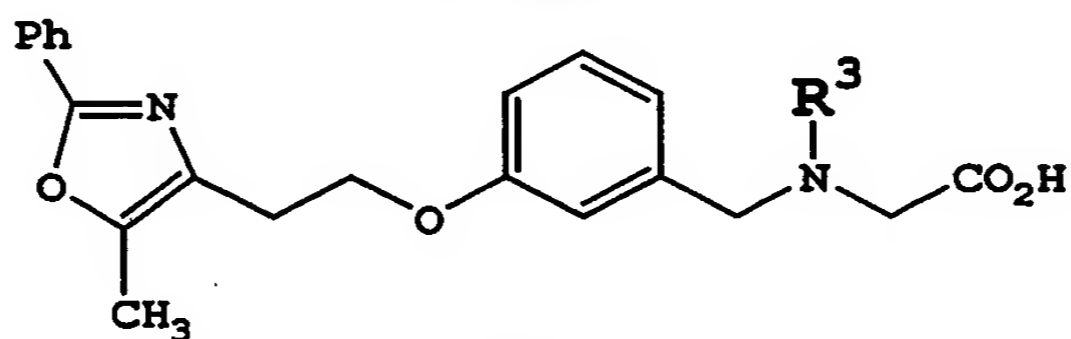
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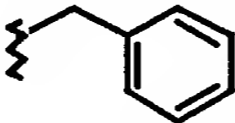
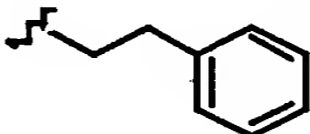
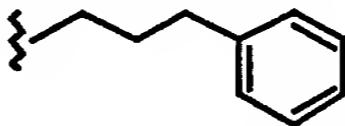
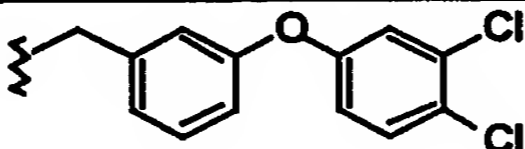
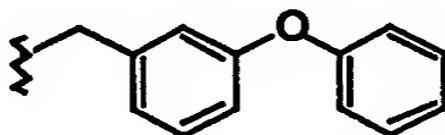
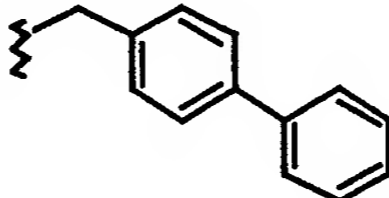
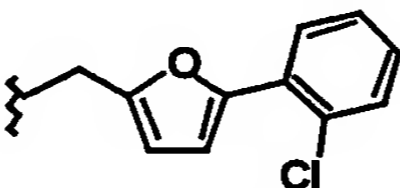
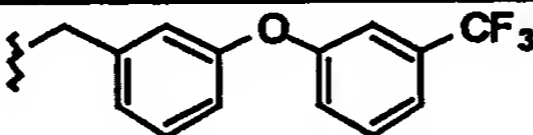
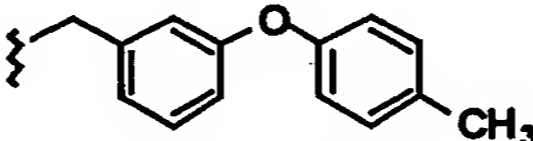
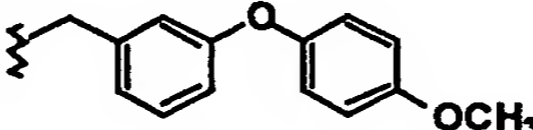
Examples 14 to 124

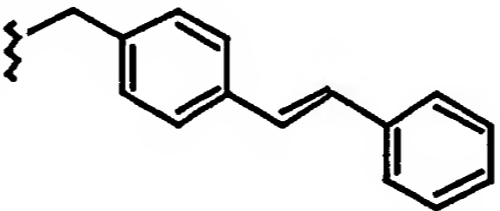
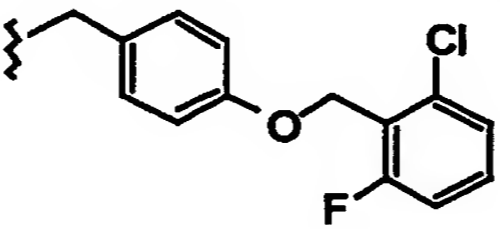
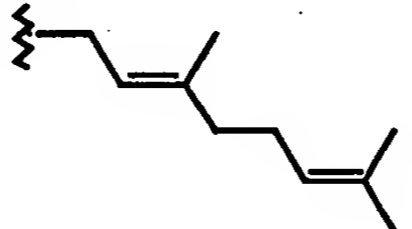
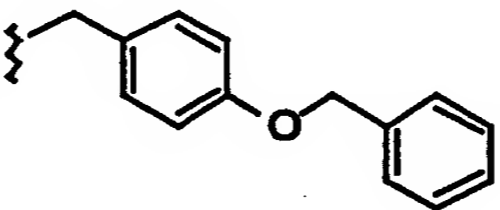
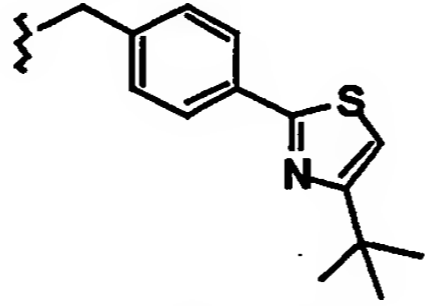
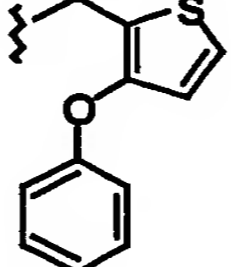
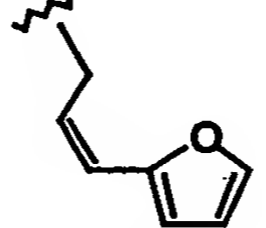
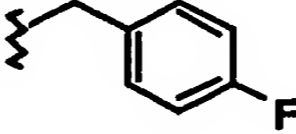
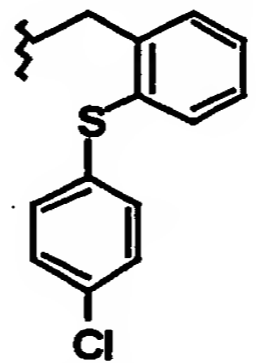
Following one of the above procedures, the following compounds of the invention were prepared:

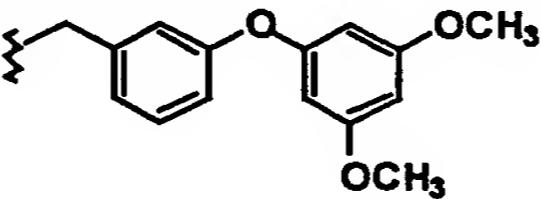
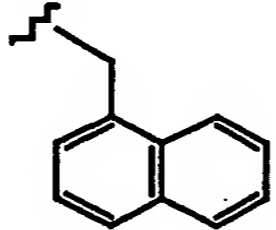
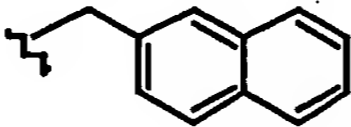
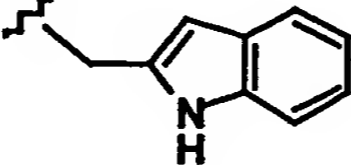
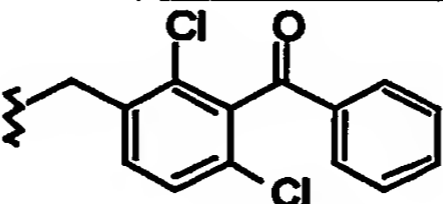
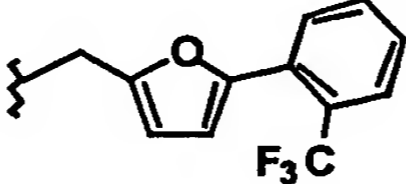
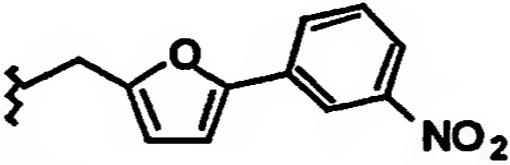
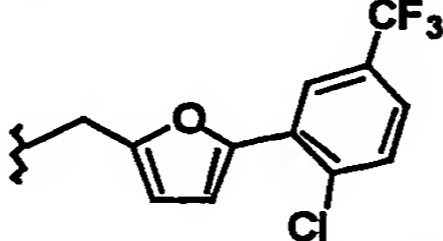
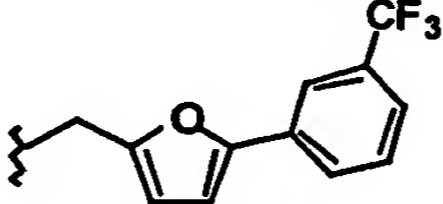
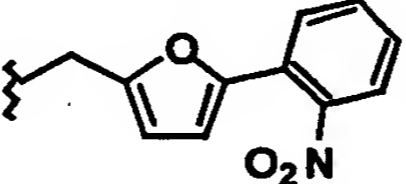
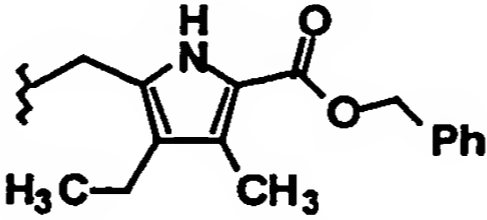
Table 1



5

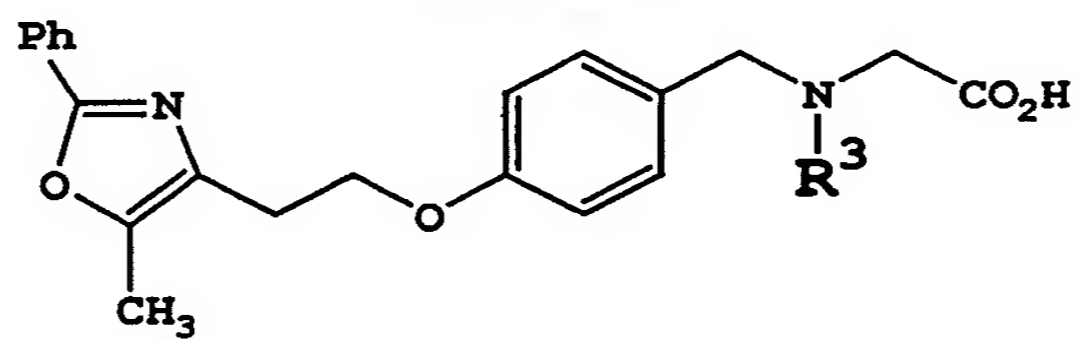
Example No.	R ³	[M+H] ⁺
14		457.3
15		471.3
16		485.3
17		617.2
18		549.3
19		533.3
20		557.3
21		617.3
22		562.7
23		579.3

Example No.	R ³	[M+H] ⁺
24		559.4
25		615.3
26		503.4
27		563.4
28		596.3
29		555.3
30		473.4
31		475.4
32		599.3

Example No.	R ³	[M+H] ⁺
33		517.4
34		507.1
35		507.1
36		496.1
37		557.1
38		591.2
39		568.2
40		625.2
41		591.2
42		568.2
43		622.3

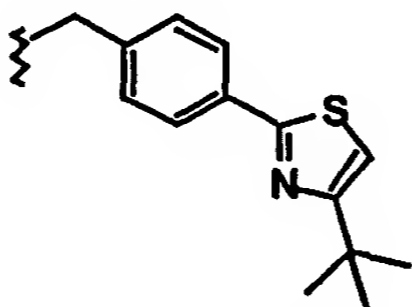
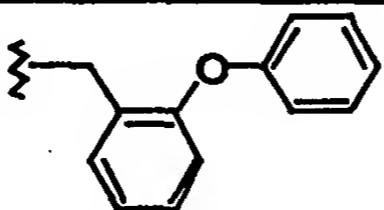
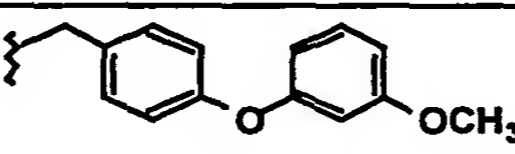
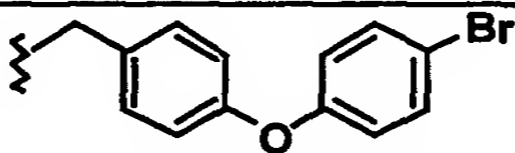
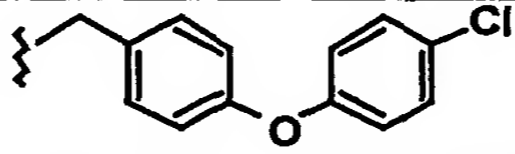
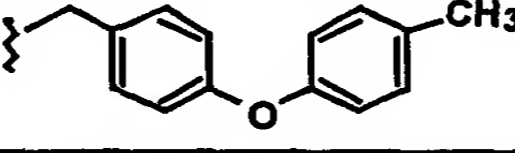
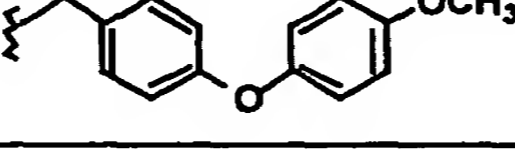
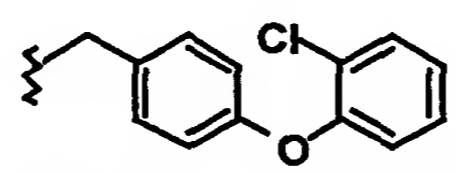
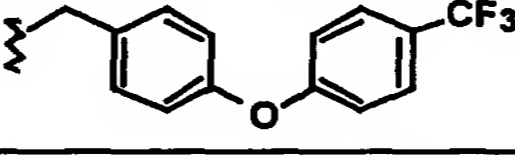
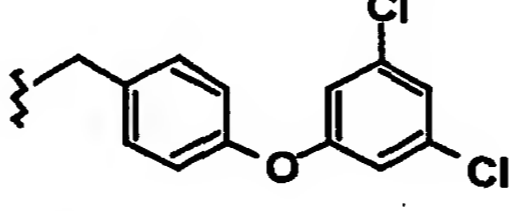
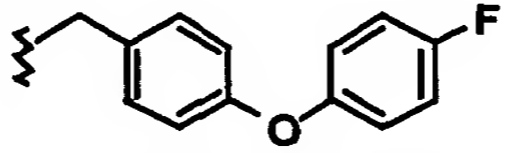
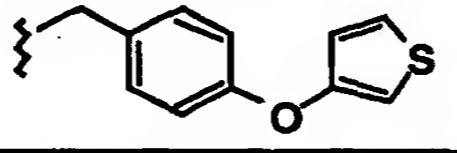
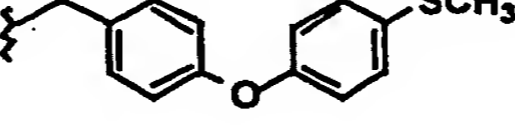
Example No.	R ³	[M+H] ⁺
65		537.3
66		537.3
67		636.2

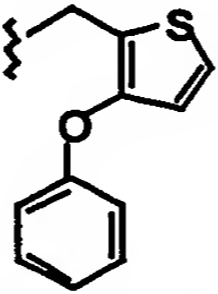
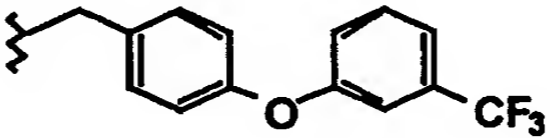
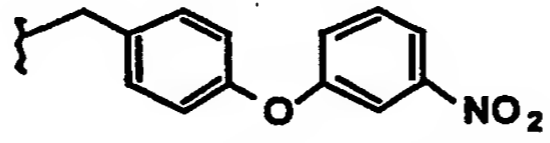
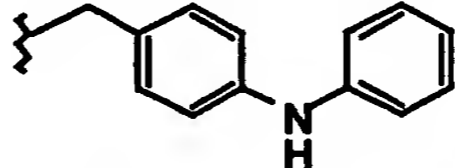
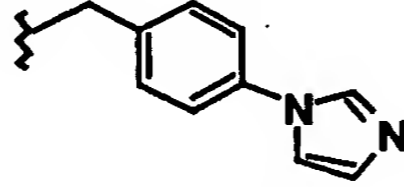
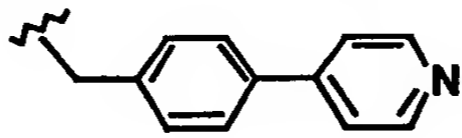
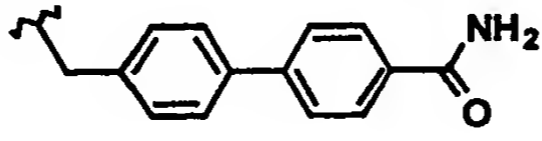
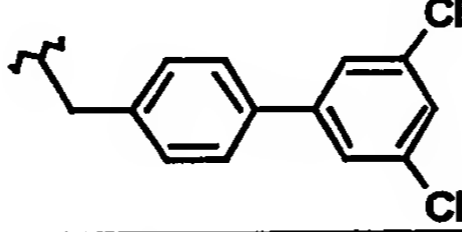
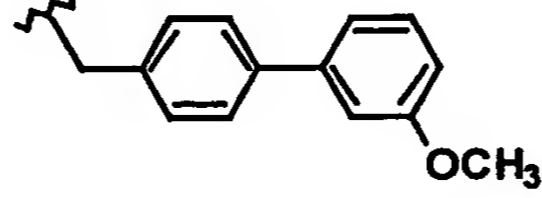
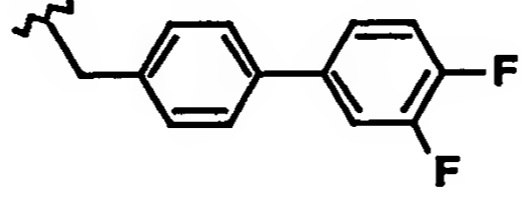
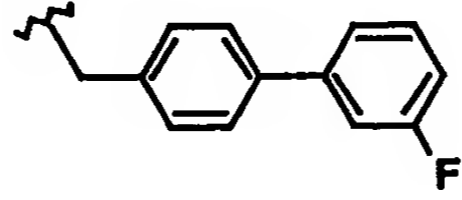
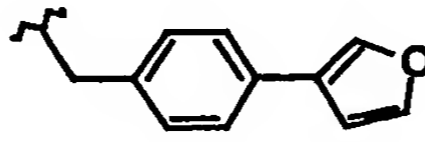
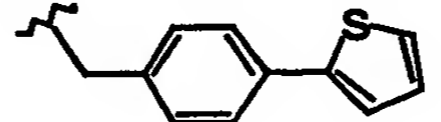
Table 2



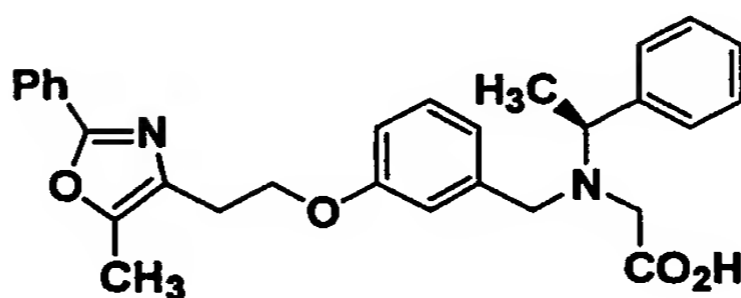
Example No.	R ³	[M+H] ⁺
68		534.2
69		547.2
70		465.4
71		533.3
72		473.3

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Example No.	R ³	[M+H] ⁺
86		596.2
87		549.3
88		635.3
89		639.2
90		583.2
91		563.2
92		635.3
93		583.2
94		617.2
95		617.1
96		567.2
97		555.1
98		595.3

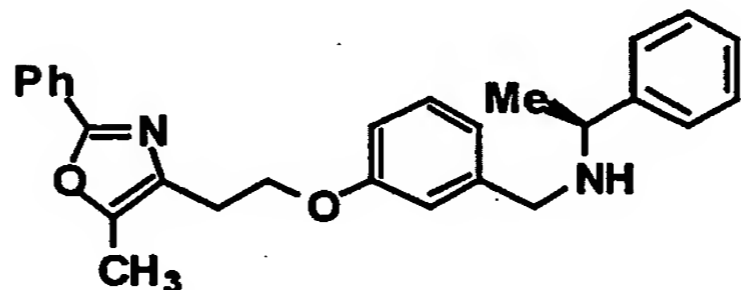
Example No.	R ³	[M+H] ⁺
99		555.2
100		617.2
101		594.2
102		548.2
103		523.3
104		534.4
105		576.2
106		601.1
107		563.2
108		609.2
109		551.2
110		523.2
111		539.2

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Example 125

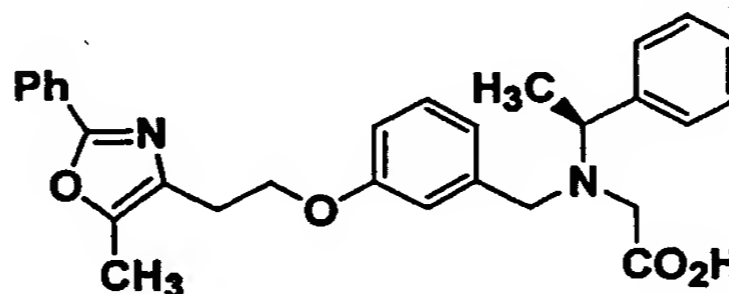
5

A.



10 A solution of Example 7 Part A aldehyde (60 mg; 0.20 mmol) and (S)- α -methyl benzylamine (30 mg; 0.24 mmol) in MeOH (1 mL) was stirred at RT for 6 h. The solution was cooled to 0°C and a pre-formed solution of NaBH₄ (9 mg; 0.24 mmol) in MeOH (0.5 mL) was added portionwise. The reaction was stirred at RT overnight, then concentrated in vacuo without heating. The residue was partitioned between aqueous NaHCO₃ and EtOAc (5 mL each). The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give title compound as an orange
15 yellow-oil (81 mg crude).

B.

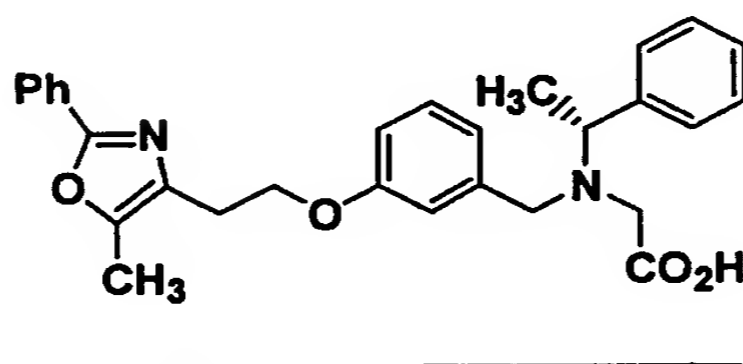


25

A solution of the Part A compound (70 mg; 0.17 mmol), tert-butyl bromoacetate (66 mg; 0.34 mmol), and iPr₂NEt in DMF (0.5 mL) was stirred at RT for 2 days. LC/MS showed that the reaction was complete and clean.

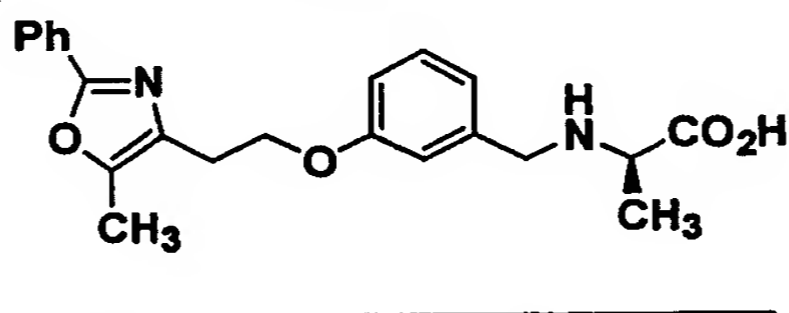
This crude product was stirred in a 1:1 solution of CHCl_3 and TFA (2 mL) for 18 h at RT. The solution was then concentrated *in vacuo* and purified by preparative reverse-phase HPLC (as in Example 10). The purified material was lyophilized from MeOH- H_2O to give the title compound (71 mg; 71%) as a white lyophilate. $[\text{M} + \text{H}]^+ = 471.2$

15



The title compound was synthesized following the same procedure as described above in Example 125 except that (S)- α -methyl benzylamine was replaced by (R)- α -methyl benzylamine in the synthesis of the part A compound. The title compound was obtained in 67% yield (66 mg) overall. $[M + H]^+ = 471.2$

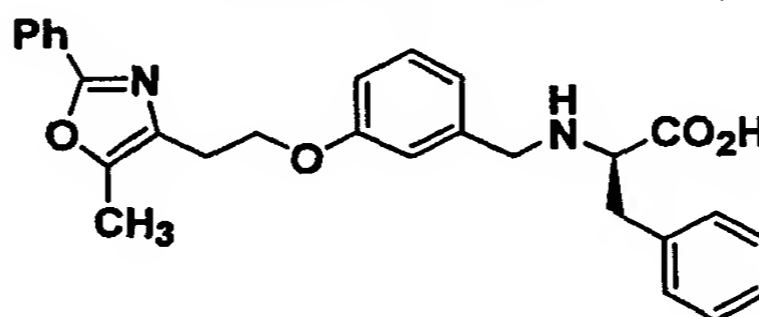
Example 127



- 120 -

in MeOH (2 mL) was stirred at RT for 4 h. NaBH₄ (12 mg, 0.0294 mmol) was added and the reaction was stirred at RT for 30 min. The reaction mixture was then concentrated in vacuo, diluted with CH₂Cl₂ (2 mL), and filtered through cotton. TFA (1 mL) was added to the filtrate and the reaction was stirred at RT overnight. The reaction mixture was concentrated in vacuo, diluted with EtOAc, washed several times with sat'd. aqueous NaHCO₃, then with brine. The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 30mm x 250mm reverse-phase column; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to provide the title compound (7.8 mg, 21%) as a white lyophilate. [M + H]⁺ = 381.1

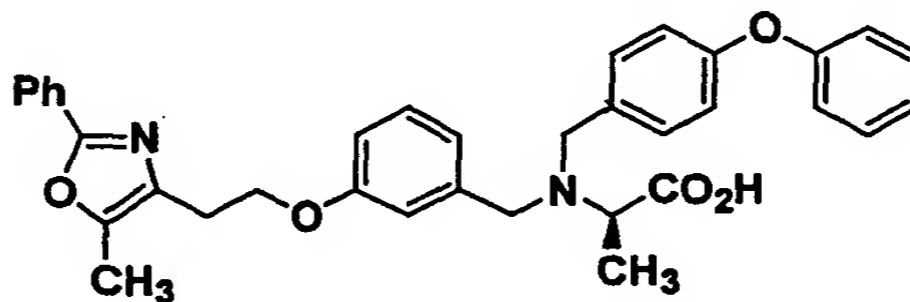
Example 128



20

Title compound (20% overall yield) was synthesized using the same procedure as described in Example 125, using D-phenylalanine tert-butyl ester hydrochloride instead of D-alanine tert-butyl ester hydrochloride. [M + H]⁺ = 457.2

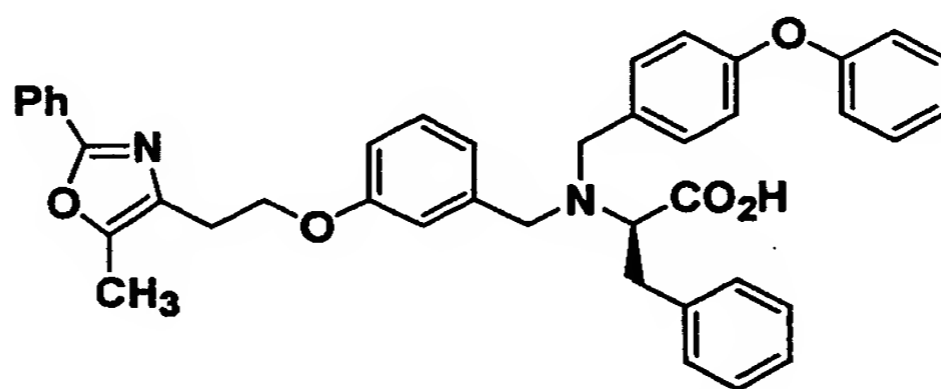
Example 129



30

A mixture of Example 7 Part A (40 mg, 0.13 mmol), D-alanine tert-butyl ester hydrochloride (31 mg, 0.17 mmol), Et₃N (6 drops) and 4A molecular sieves in MeOH (2 mL) was stirred at RT for 4 h. NaBH₄ (15 mg, 3 equiv) was added and the mixture was stirred at RT for 30 min, then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (2 mL) and filtered. To the filtrate in a vial were added 4-phenoxybenzaldehyde (77 mg, 0.39 mmol) and NaBH(OAc)₃ (138 mg, 0.65 mmol). The reaction was stirred at RT for 18 h. The reaction mixture was chromatographed on SiO₂ using hexanes/EtOAc (9:1 to 4:1) to obtain the pure tert-butyl ester. This material was dissolved in CH₂Cl₂ (2 mL) and TFA (1 mL) was added slowly. The solution was stirred at RT overnight, then was concentrated *in vacuo*. The residue was redissolved in CH₂Cl₂ and filtered through solid NaHCO₃ to remove residual TFA. This solution was further diluted with CH₂Cl₂, washed with 1 M aq NaHSO₄ and brine, dried (MgSO₄), filtered and concentrated *in vacuo* to obtain the title compound (9.1 mg, 12%). [M + H]⁺ = 563.2

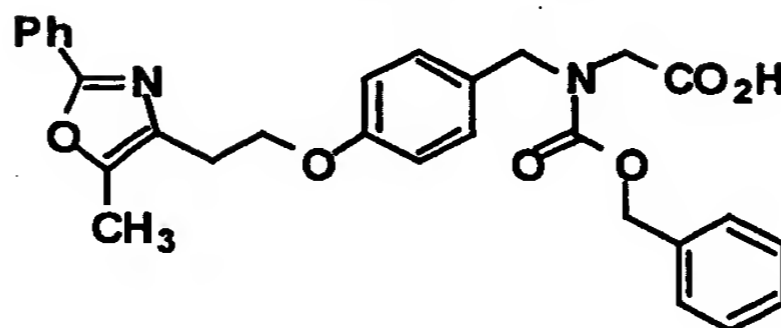
Example 130



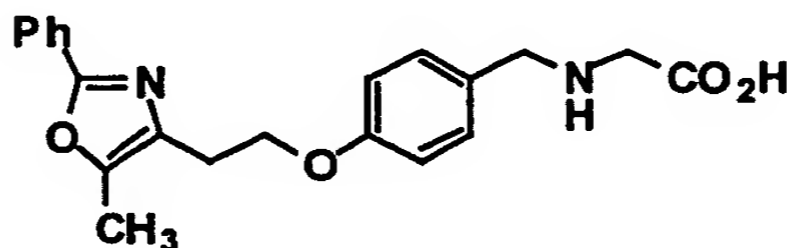
25

The title compound (13% overall yield) was synthesized using the same procedure as described in Example 127, using D-phenyl-alanine tert-butyl ester hydrochloride instead of D-alanine tert-butyl ester hydrochloride. [M + H]⁺ = 639.2

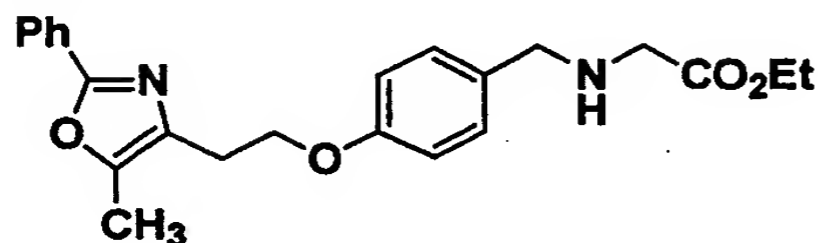
30

Example 136

A.

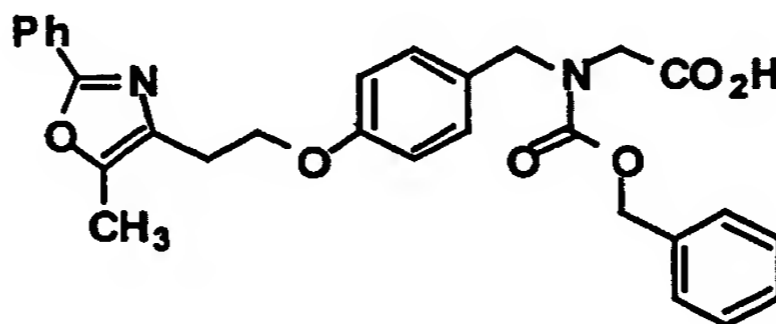


A solution of the secondary amine ethyl ester (72 mg; 0.183 mmol)



(prepared as described in Example 3 Part A) in MeOH (2 mL) and aqueous NaOH (2 mL of a 1M solution) was heated under reflux for 12 h. The pH of the solution was adjusted to 5 (with aqueous 1M NaOH and 1M HCl), upon which a colorless solid precipitated. This was filtered off and the filtrate was extracted with EtOAc (3x); the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude title amino acid as a colorless solid (97 mg).

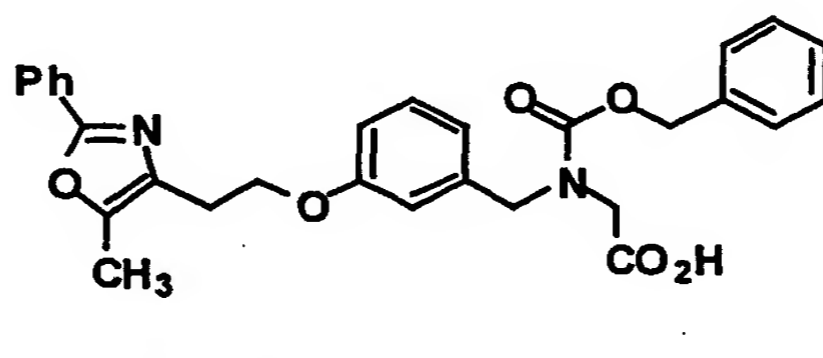
B.



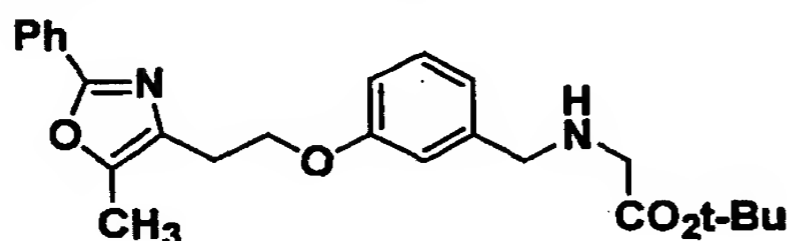
To a solution of the Part A amino acid (15 mg; 0.04 mmol) in dioxane:H₂O (1:1, 8 mL) was added K₂CO₃ (22 mg;

0.16 mmol) followed by benzyl chloroformate (15 mg; 0.09 mmol). The reaction was stirred overnight, then concentrated *in vacuo* and acidified with excess aqueous 1M HCl. This was extracted with EtOAc (3x); the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo* to give title compound (13 mg; 63%) as a colorless solid. $[M + H]^+ = 501.3$

Example 137



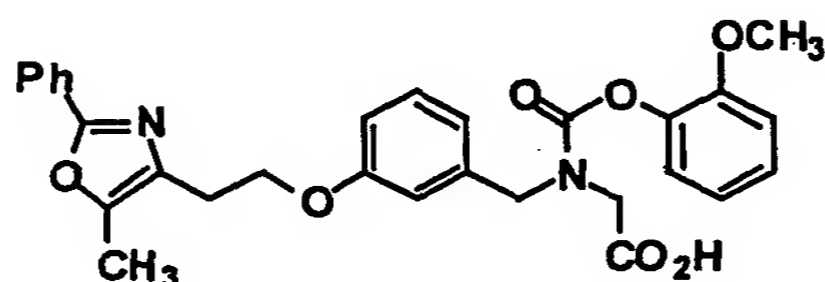
To a 0°C solution of the amino-tert-butyl ester (75 mg; 0.18 mmol)



(prepared as described in Example 7 Part B), in CH₂Cl₂ (1 mL) was added CbzCl (28 μL; 0.20 mmol), followed by Et₃N (54 μL; 0.39 mmol). The reaction was allowed to warm to RT and then stirred at RT overnight for 18 h. Aqueous NaHCO₃ (2 mL of a 10% solution) was added and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The crude carbamate-ester was dissolved in CHCl₃ (3 mL) and TFA (1 mL); the solution was stirred at RT for 24 h, then concentrated *in vacuo*. The crude carbamate-acid was purified by reverse-phase preparative HPLC on a C-18 column (continuous gradient over 14 min; 4 min hold time; flow rate = 20 mL/min from 1:1 A:B to 100% B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA). The product was

lyophilized from MeOH/H₂O to give title compound as a white lyophilate. $[M + H]^+ = 501.3$.

Example 138



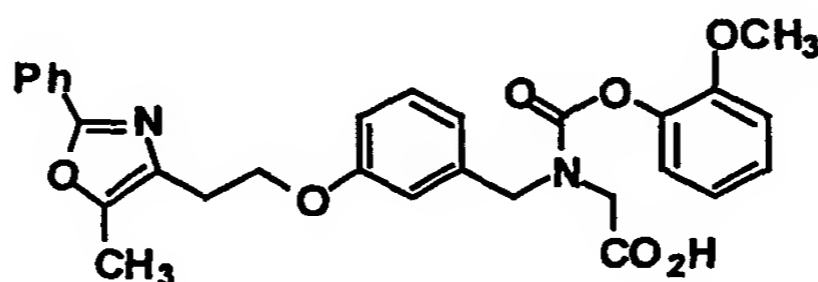
5

A. The required aryl chloroformates (where not commercially available) were prepared according to the following general procedure, which is exemplified by the synthesis of 2-methoxy phenyl chloroformate:

A solution of 2-methoxyphenol (2 g, 16.1 mmol), N,N-dimethylaniline (1.95 g, 16.1 mmol), phosgene (8.34 mL of a 1.93 M solution in toluene, 16.1 mmol) and a catalytic amount of DMF in chlorobenzene (5 mL) was stirred in a pressure tube for 2 h at 80°C. The organic layer was separated and concentrated in vacuo. The residue was distilled (Buchi Kugelrohr; bp = 115°C @ 10 mm Hg) to provide 2-methoxyphenyl chloroformate (1.5g; 50%) as a clear oil.

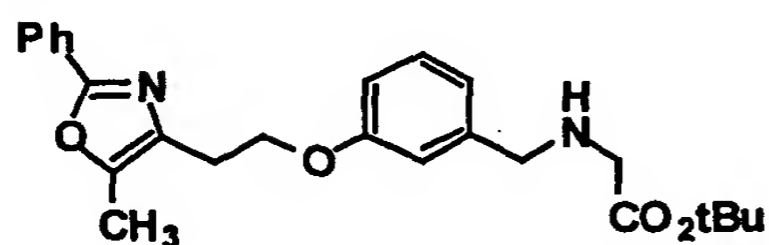
20

B.



25

A solution of the amino-t-butyl ester (20 mg, 0.05 mmol),



(prepared as described in Example 7 Part B),
2-methoxyphenyl chloroformate (8 mg, 0.05 mmol; prepared
as above) and polyvinylpyridine (Aldrich; 16 mg, 0.3
mmol) in CH_2Cl_2 (1 mL) was stirred for 30 min at RT.

- 5 Amine resin WA21J (Supelco; 200 mg) was added and the
mixture was stirred at RT for 30 min in order to remove
unreacted chloroformate. The reaction mixture was
filtered and concentrated in vacuo to give the desired 2-
methoxyphenyl carbamate-ester.

- 10 The ester was treated with a solution of 30% TFA in
 CH_2Cl_2 (5 mL) overnight. Volatiles were removed in vacuo
to give the crude acid. This material was purified via
solid-phase extraction using an anion exchange column
(CHQAX13M6 column; United Technologies; 3 g of sorbent in
15 a 6 mL column) by the exemplary procedure outlined below.

1) The column was conditioned with MeOH (10 mL) and CH_2Cl_2
(10 mL).

- 20 2) The crude acid was dissolved in a minimal volume of
 CH_2Cl_2 and loaded onto the SAX column.

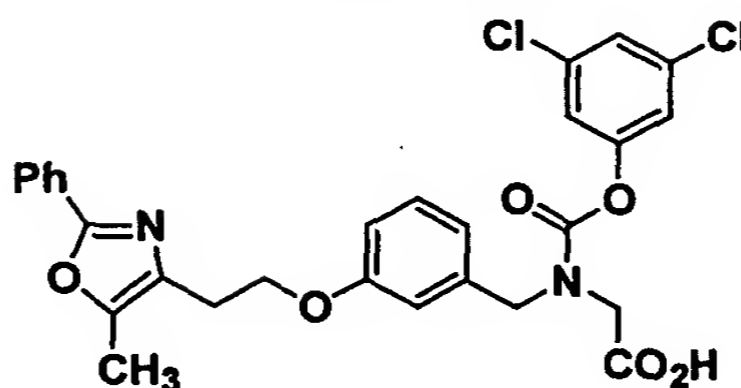
3) The cartridge was washed with CH_2Cl_2 (10 mL),
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10 mL of a 4:1 $\text{CH}_2\text{Cl}_2:\text{MeOH}$ solution).

25

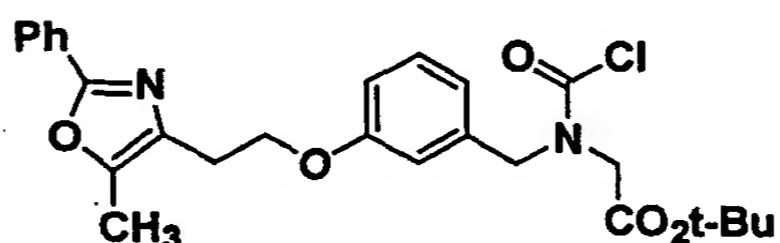
4) The product was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10 mL of a 4:1
 $\text{CH}_2\text{Cl}_2:\text{MeOH}$ solution).

- 30 The product-containing fractions were concentrated
in vacuo on a Speed Vac to afford title compound as an
oil. Analytical reverse-phase HPLC (standard conditions)
indicated that the purity of the product was 90%. In
addition LC/MS gave the correct molecular ion $[(M+H)^+ =$
517.3] for the desired title compound.

35

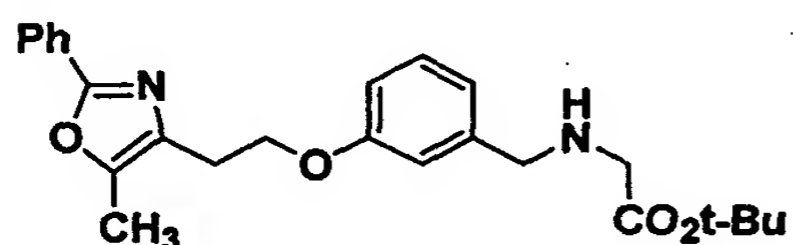
Example 139

A.



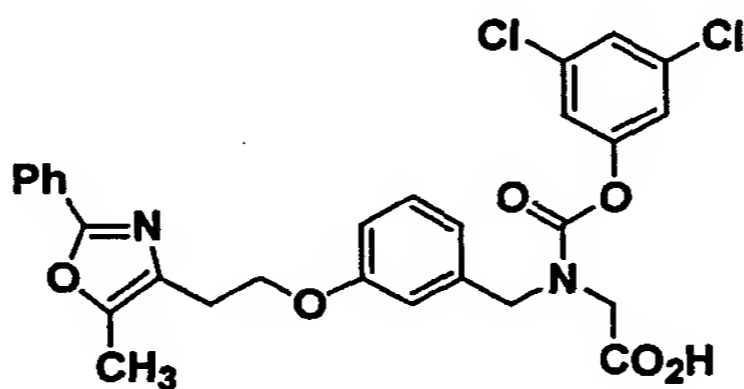
5

Phosgene (0.21 mL of a 1.93 M solution in toluene; 0.40 mmol) was added dropwise to a solution of the amino-
 10 tert-butyl ester (100 mg, 0.24 mmol)



(prepared as described in Example 7 Part B),
 and Et₃N (30.3 mg; 0.30 mmol) in 3 mL CH₂Cl₂ at -5°C. The
 reaction mixture was stirred at RT for 2 h. The mixture
 15 was concentrated in vacuo to give the crude product which
 was chromatographed (SiO₂; hexane/EtOAc 1:5) to provide
 title compound (0.105 g, 91%).

B.



20

The title compound was prepared as part of a
 solution phase library run using the following exemplary
 25 procedure.

5

- 10

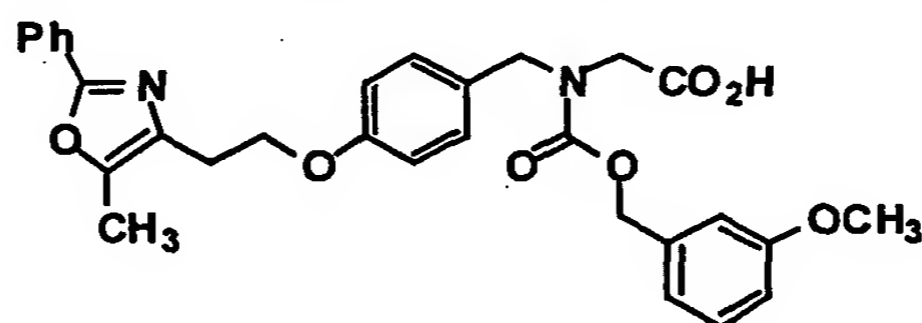
20

- 30

5) The product was eluted with 2% TFA in CH₂Cl₂ (10 mL)

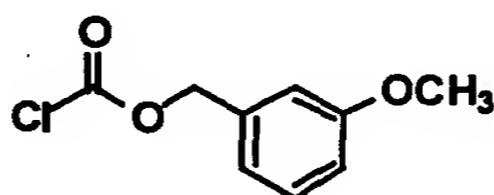
The product-containing fractions were concentrated
in vacuo using a Speed Vac for 16 h to afford the
purified product (20 mg, 80%) as a solid. Reverse phase
HPLC analysis (YMC S5 ODS 4.6 x 33 mm column, continuous
gradient from 50% A to 100% B for 2 min at a flow rate of
5 mL/min [Solvent A = 10%MeOH/90%H₂O/0.2% H₃PO₄; Solvent
B = 90%MeOH/10% H₂O/0.2% H₃PO₄]) indicated that the
product purity was 96%. In addition, LC/MS gave the
correct molecular ion [(M+H)⁺ = 555.2] (electrospray) for
the title compound.

15

Example 140

Benzyol chloroformates were synthesized by the
following general procedure, as exemplified by m-methoxy
benzyol chloroformate:

A.



25

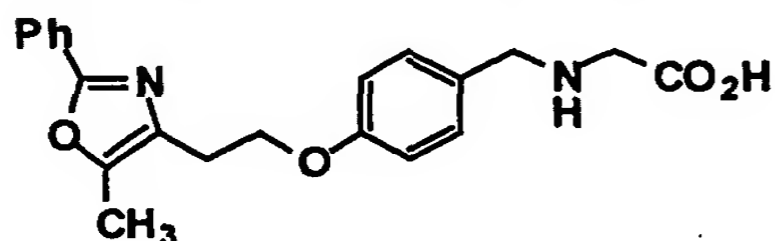
To a solution of 3-methoxybenzyl alcohol (2.0 g;
7.24 mmol), N,N-dimethylaniline (0.877 g; 7.24 mmol) in
anhydrous ether (5 mL) was added phosgene dropwise (3.8
mL of a 1.93 M solution in toluene; 7.3 mmol) at 0°C.
The reaction mixture was stirred at 0°C for 2 h, after

5

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)COC(=O)NCC(=O)OC4=CC=C(C=C4)OC)C

The title compound was prepared as part of a solution phase library which was run using the following standard procedure.

15



20

25

1) The column was conditioned with MeOH (10 mL) and CH₂Cl₂ (10 mL)

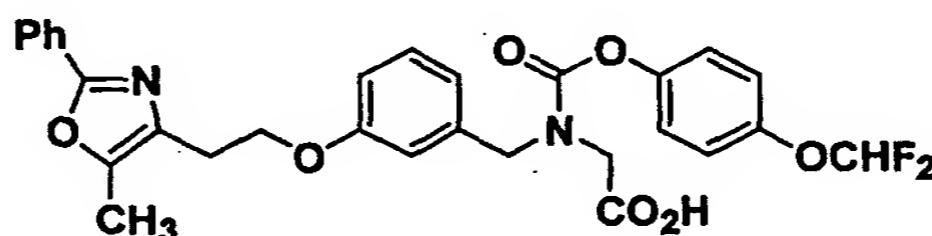
2) The residue was dissolved in a minimal volume of CH_2Cl_2 and loaded onto the SAX column.

3) The cartridge was washed successively with CH_2Cl_2 (10 mL), 20% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (10 mL).

4) The product was eluted with a solution of 20% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (10 mL).

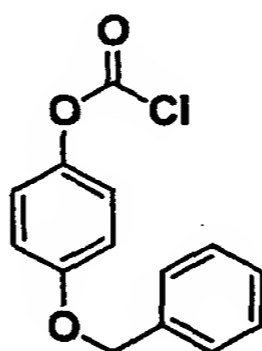
10 The product-containing fractions were concentrated in vacuo using a Speed Vac to afford the title compound. Reverse Phase HPLC analysis using standard conditions indicated that the product purity was 90%. In addition, LC/MS (electrospray) gave the correct molecular ion
15 $[(M+H)^+ = 531.3]$ for the desired title compound.

Example 141



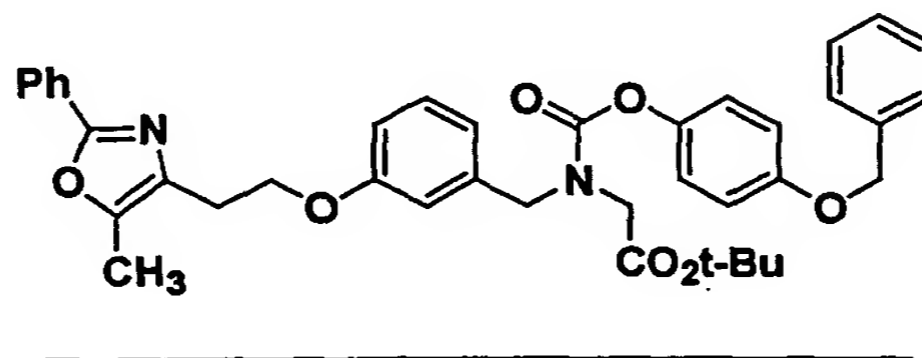
20

A.



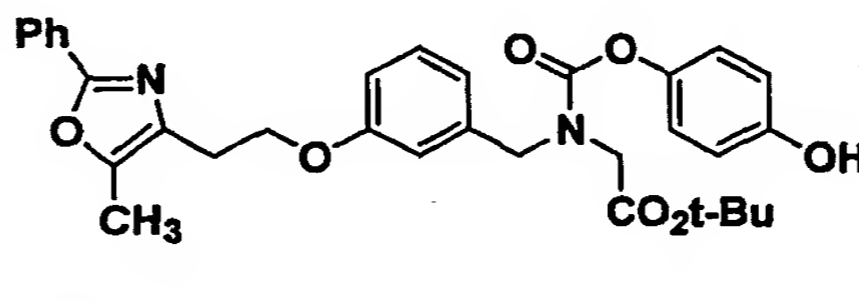
25 A solution of 4-(benzyloxy)phenol (2.0 g; 9.99 mmol), N,N-dimethylaniline (1.21 g; 9.99 mmol), phosgene (5.2 mL of a 1.95 M solution in toluene; 10 mmol) and a catalytic amount of DMF in chlorobenzene (5 mL) was heated at 80°C in a pressure tube for 2.5 h. The mixture
30 was allowed to cool to RT. The upper clear solution was

B.

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=CC=C3CNCC(=O)OC(C)C)C

(prepared as described in Example 7 Part B),
in CH₂Cl₂ (5 mL). The reaction was stirred at RT for 15
15 min. Resin-bound amine (WA21J, Supelco; 150 mg) was
added to the mixture. The reaction mixture was stirred
for another 15 min. The resin-bound amine and
polyvinylpyridine were filtered off and the filtrate was
concentrated *in vacuo* to give the crude product. The
20 crude product was chromatographed (SiO₂; hexane/EtOAc
1:4) to provide title compound (0.30 g, 70%).

C.

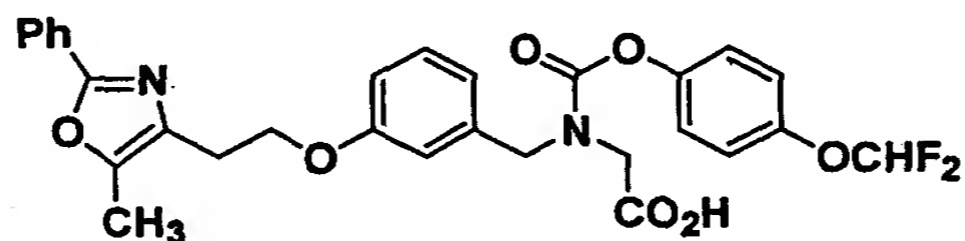


- 133 -

The palladium catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the crude title *t*-butyl ester (240 mg, 90%) which was used without further purification in the next step.

5

D.

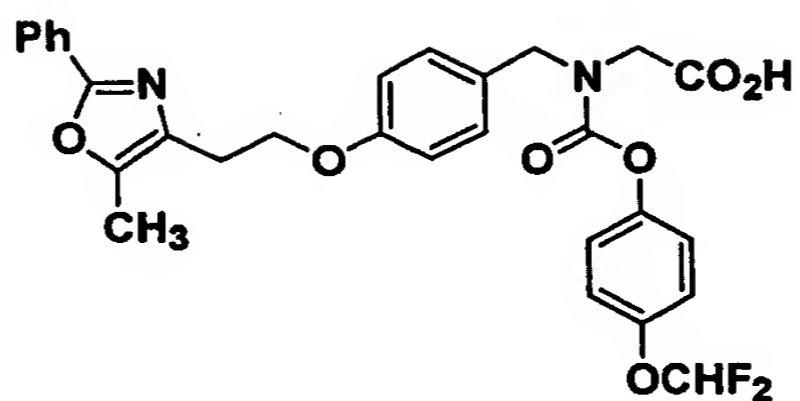


10 The solution of Part C phenol-*tert*-butyl ester (50 mg; 0.089 mmol), catalytic Bu₄NBr (1.5 mg, 0.0047 mmol), aq NaOH (0.7 mL of a 1 M solution) and isopropanol (2 mL) in a pressure tube was cooled to -50°C. Freon gas was bubbled into the solution for 1 min. The tube was sealed
15 and heated to 80°C for 12 h. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to give an oil, which was then treated with a solution of 30% TFA in CH₂Cl₂ overnight. Volatiles were
20 removed *in vacuo* and the residue was purified using preparative HPLC (YMC S5 ODS 30 x 250mm reverse phase column; 30 minute continuous gradient from 70:30 A:B to 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA, and B = 90:10:0.1 MeOH:H₂O:TFA) to afford the desired title
25 product (14 mg; 28%). Reverse Phase HPLC analysis indicated that the product purity was 97%. In addition LC/MS (electrospray) gave the correct molecular ion [(M+H)⁺ = 553.1] for the desired compound.

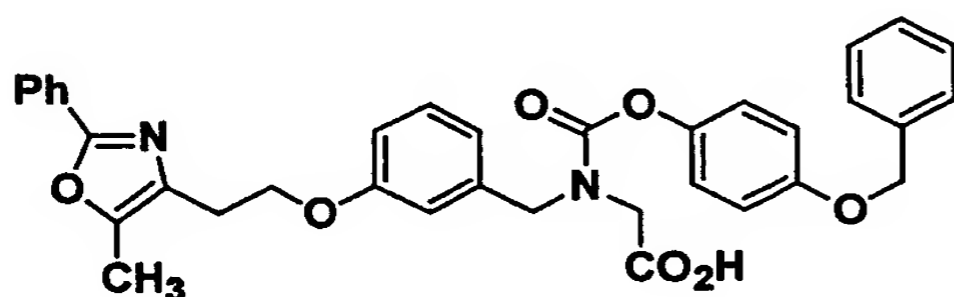
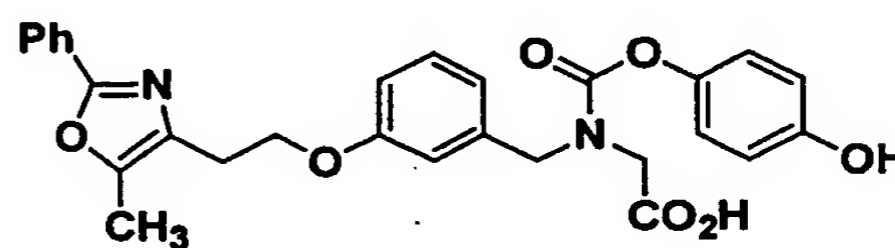
30

Example 142

Following the Example 141 procedure, the analogous compound was prepared [(M+H)⁺ = 553.2]:



Intermediates corresponding to Example 141 Parts B and C were deprotected using the same TFA/ CHCl_3 procedure as above and purified as usual to give the following
5 analogs:

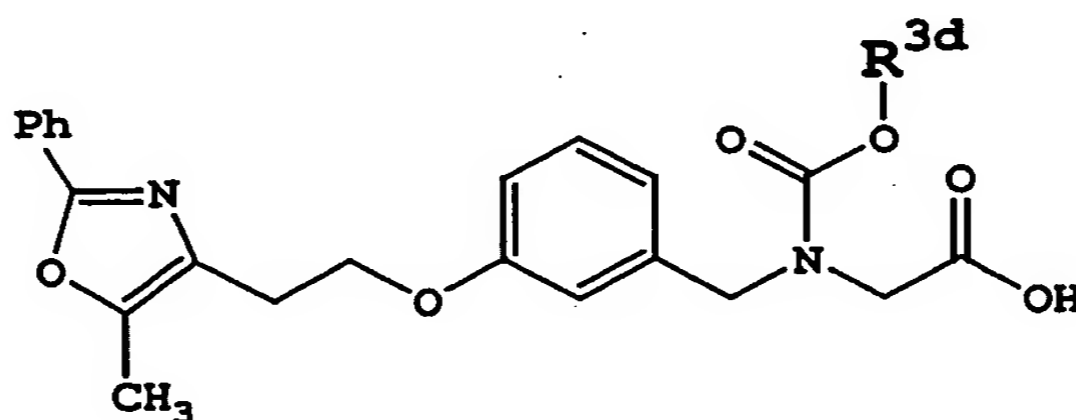
Example 143Example 144

Example 143: $[\text{M} + \text{H}]^+ = 593.4$

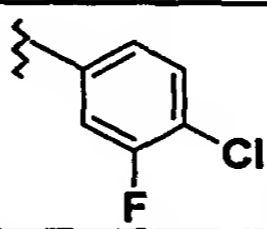
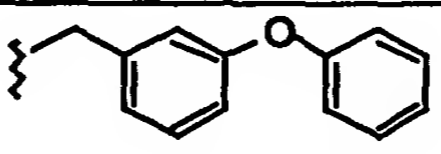
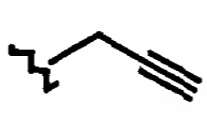
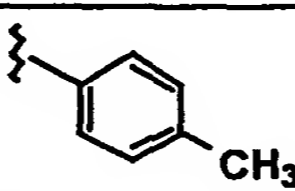
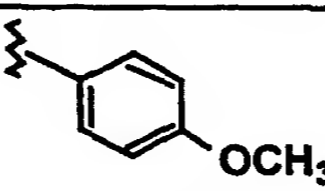
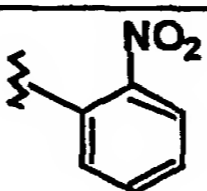
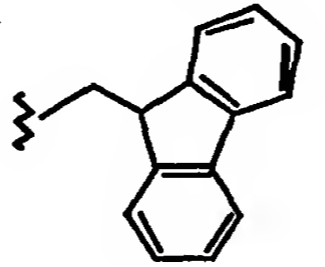
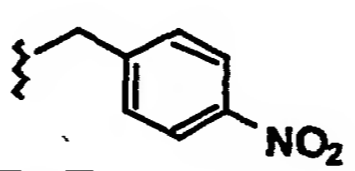
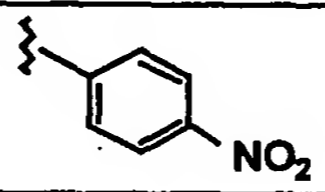
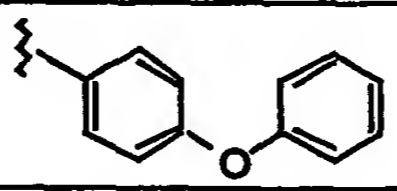
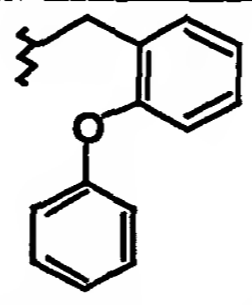
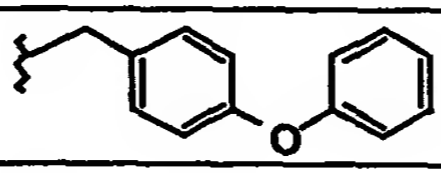
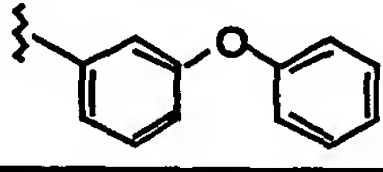
10 Example 144: $[\text{M} + \text{H}]^+ = 503.1$

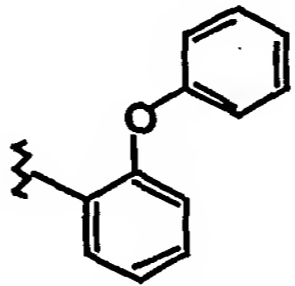
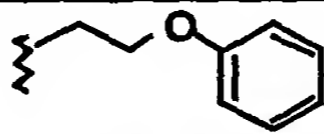
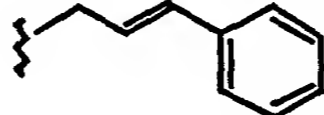
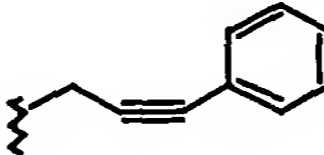
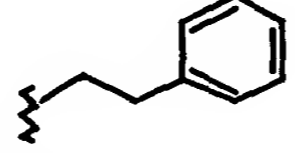
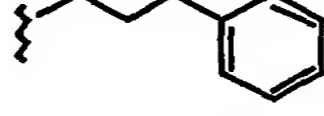

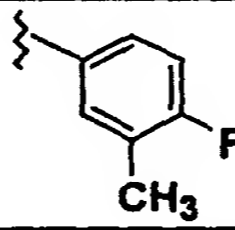
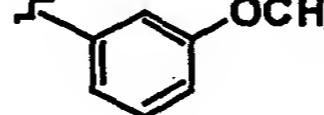
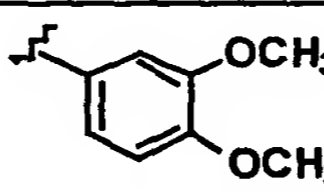
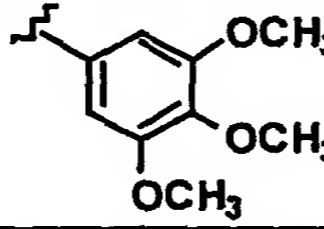
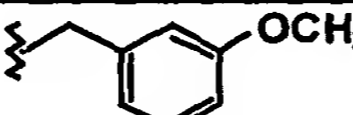
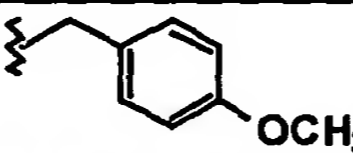
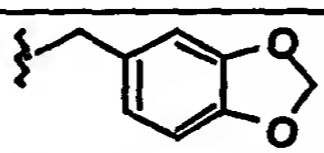
Examples 145 to 305

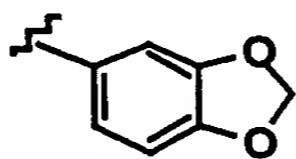
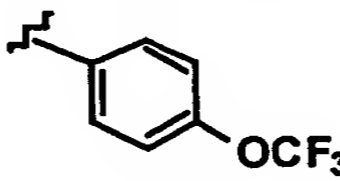
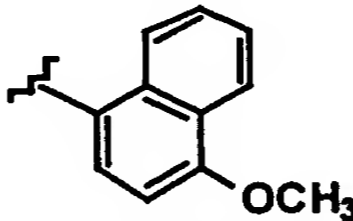
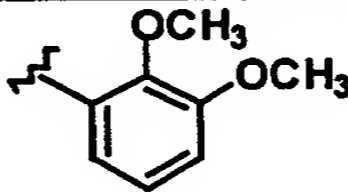
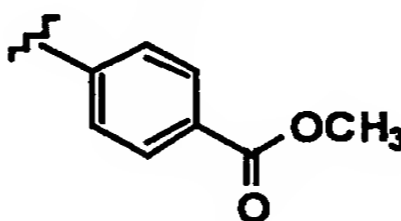
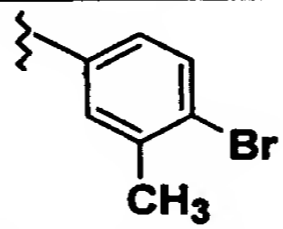
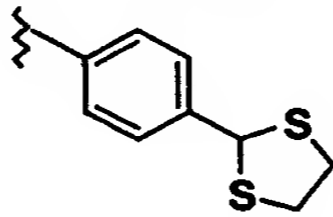
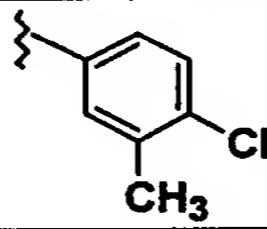
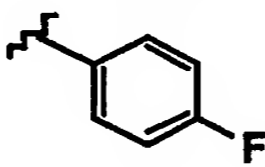
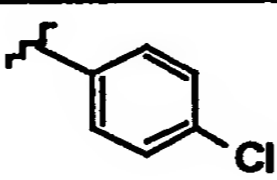
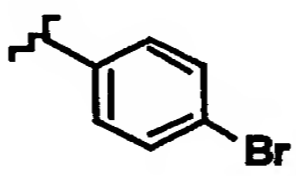
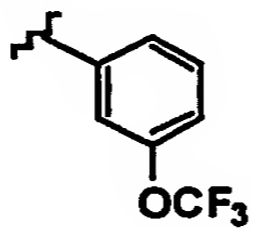
The following carbamate-acid analogs in Tables 4 and
15 5 were synthesized according to one of the above methods:

Table 4

Example No.	R^{3d}	$[\text{M} + \text{H}]^+$
145		487.2

Example No.	R ^{3d}	[M+H] ⁺
146		539.3
147		593.2
148		449.3
149		501.3
150		517.2
151		532.2
152		589.3
153		546.3
154		532.2
155		579.2
156		593.2
157		593.3
158		579.2

Example No.	R ^{3d}	[M+H] ⁺
159		579.2
160		531.2
161		527.2
162		525.2
163		515.2
164		529.2
165		527.2
166		519.3
167		517.3
168		547.3
169		577.3
170		531.3
171		531.3
172		545.3

Example No.	R ^{3d}	[M+H] ⁺
173		531.3
174		571.2
175		567.3
176		547.3
177		545.3
178		579.2
179		591.2
180		535.2
181		505.2
182		521.1
183		566 + 588
184		571.1

- 139 -

- 140 -

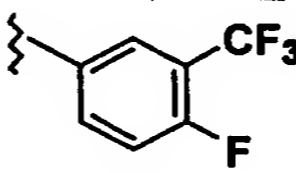
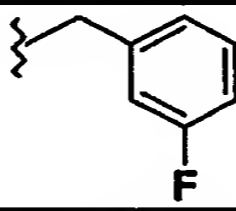
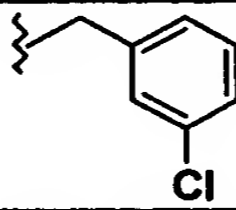
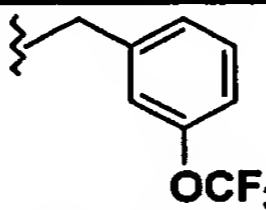
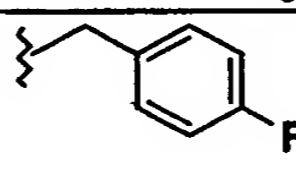
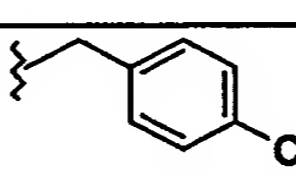
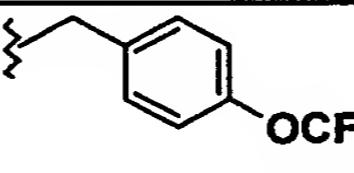
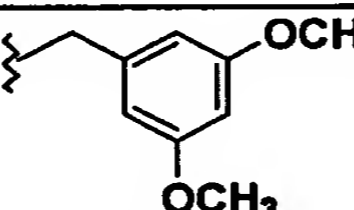
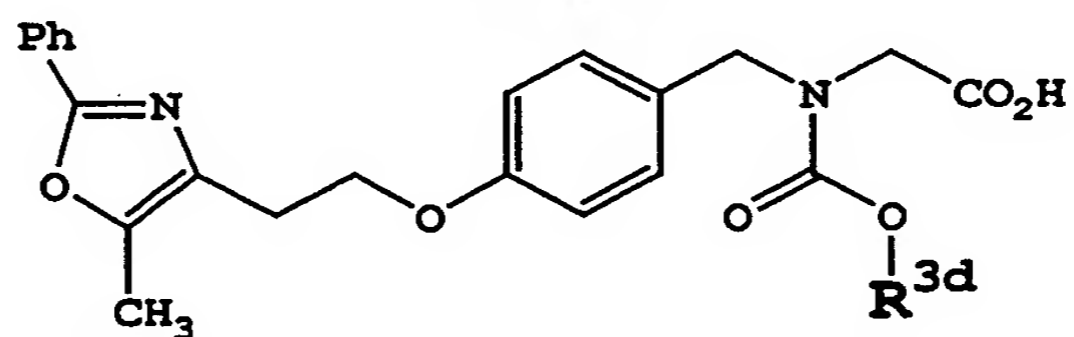
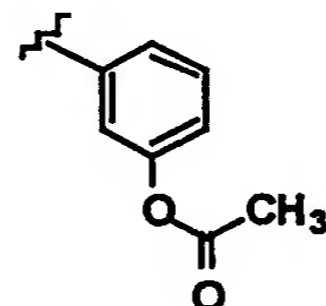
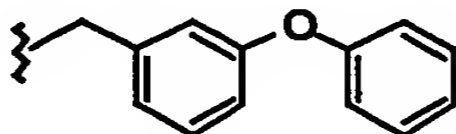
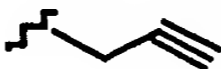
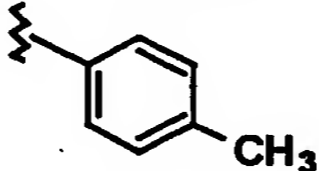
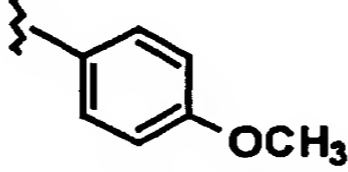
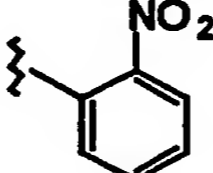
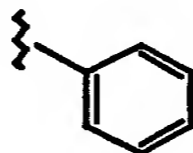
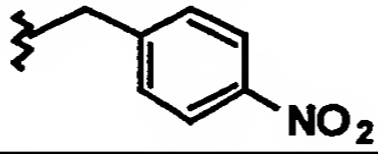
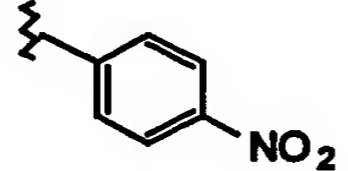
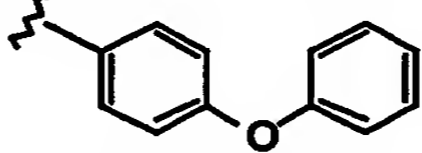
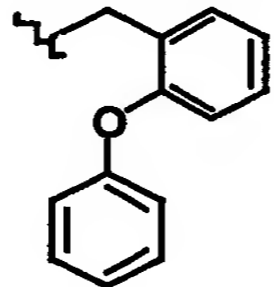
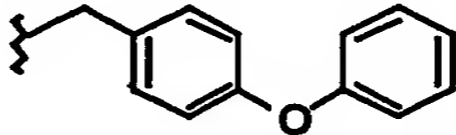
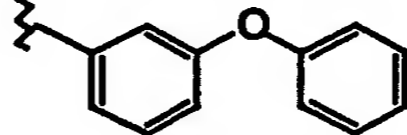
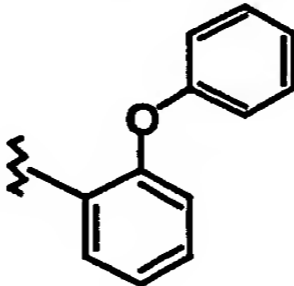
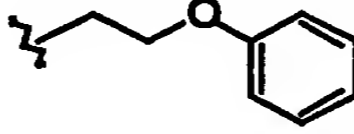
Example No.	R ^{3d}	[M+H] ⁺
218		573.1
219		519.2
220		535.2
221		585.2
222		519.2
223		535.2
224		585.2
225		561.2

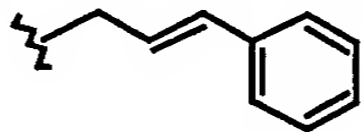
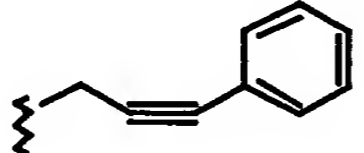
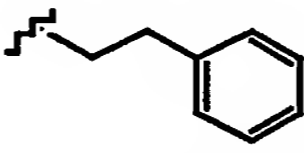
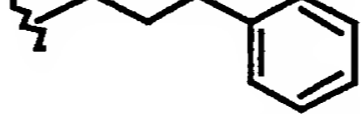
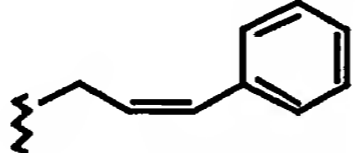
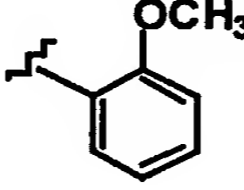
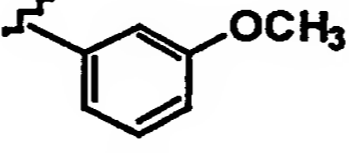
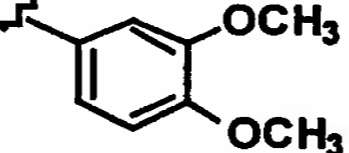
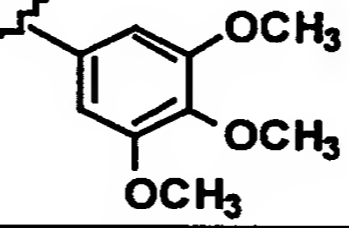
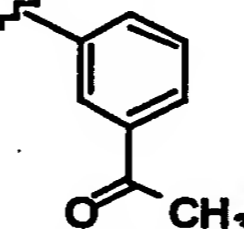
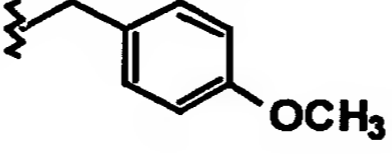
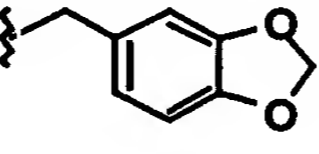
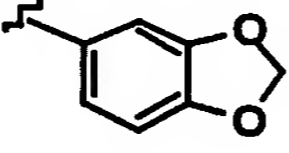
Table 5

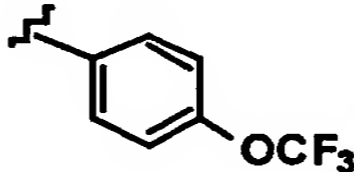
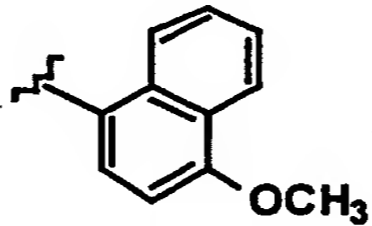
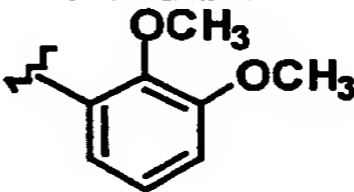
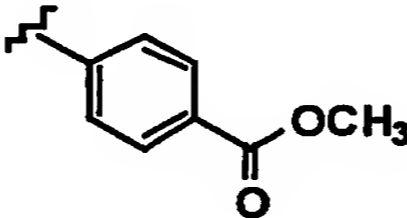
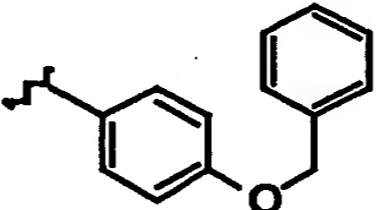
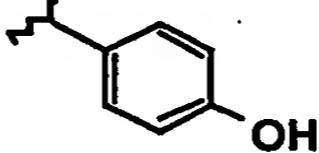
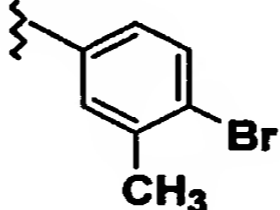
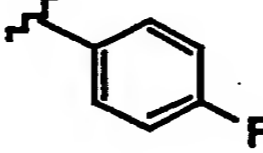
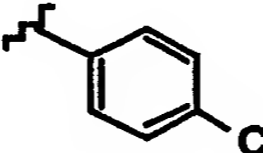
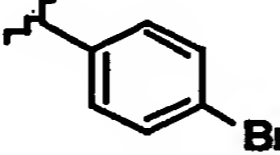


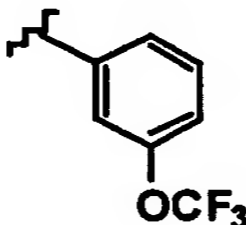
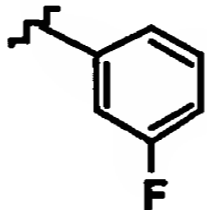
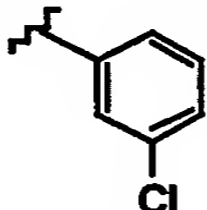
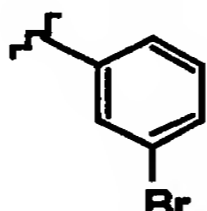
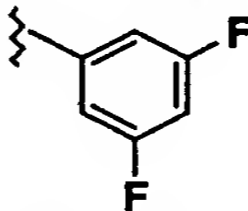
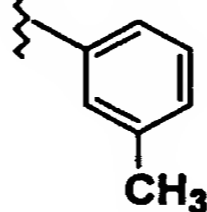
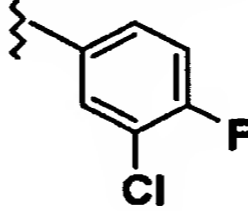
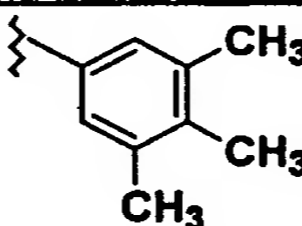
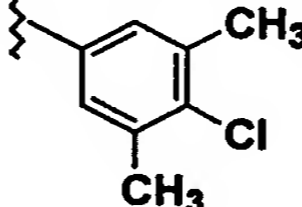
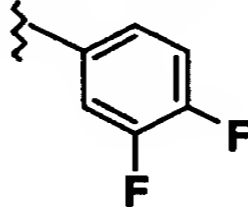
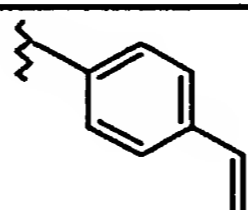
5

Example No.	R ^{3d}	[M+H] ⁺
226		545.2

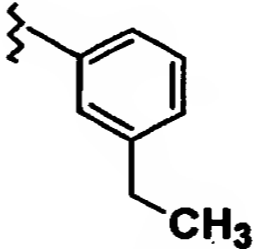
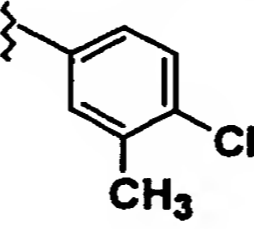
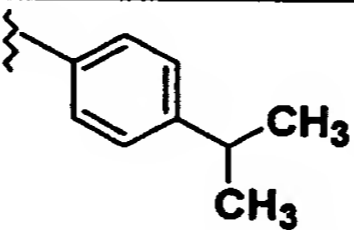
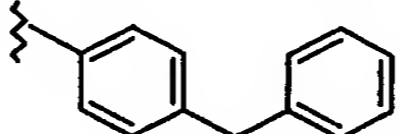
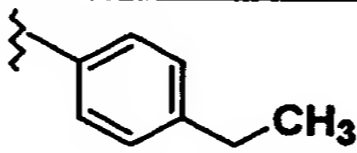
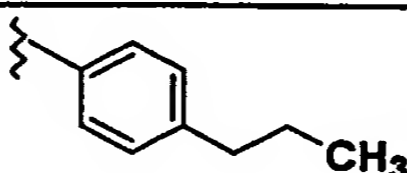
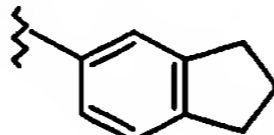
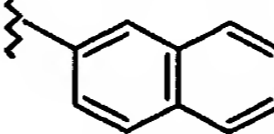
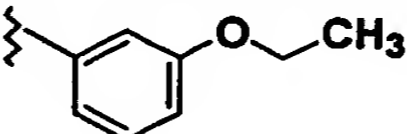
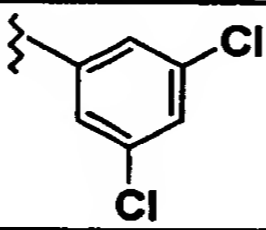
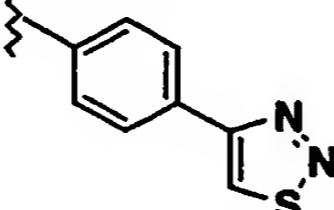
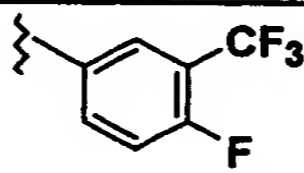
Example No.	R ^{3d}	[M+H] ⁺
227		593.1
228		449.2
229		501.2
230		517.2
231		532.2
232		487.3
233		546.3
234		532.2
235		579.2
236		593.2
237		593.3
238		579.2
239		579.2
240		531.2

Example No.	R ^{3d}	[M+H] ⁺
241		527.2
242		525.2
243		515.2
244		529.2
245		527.2
246		517.3
247		517.3
248		547.3
249		577.3
250		543.1
251		531.3
252		545.3
253		531.3

Example No.	R ^{3d}	[M+H] ⁺
254		571.2
255		567.3
256		547.3
257		545.3
258		593.4
259		503.2
260		579.2
261		505.2
262		521.1
263		566/567

Example No.	R ^{3d}	[M+H] ⁺
264		571.1
265		505.2
266		521.1
267		566/567.0
268		523.3
269		501.3
270		539.2
271		529.3
272		549.2
273		523.2
274		513.3

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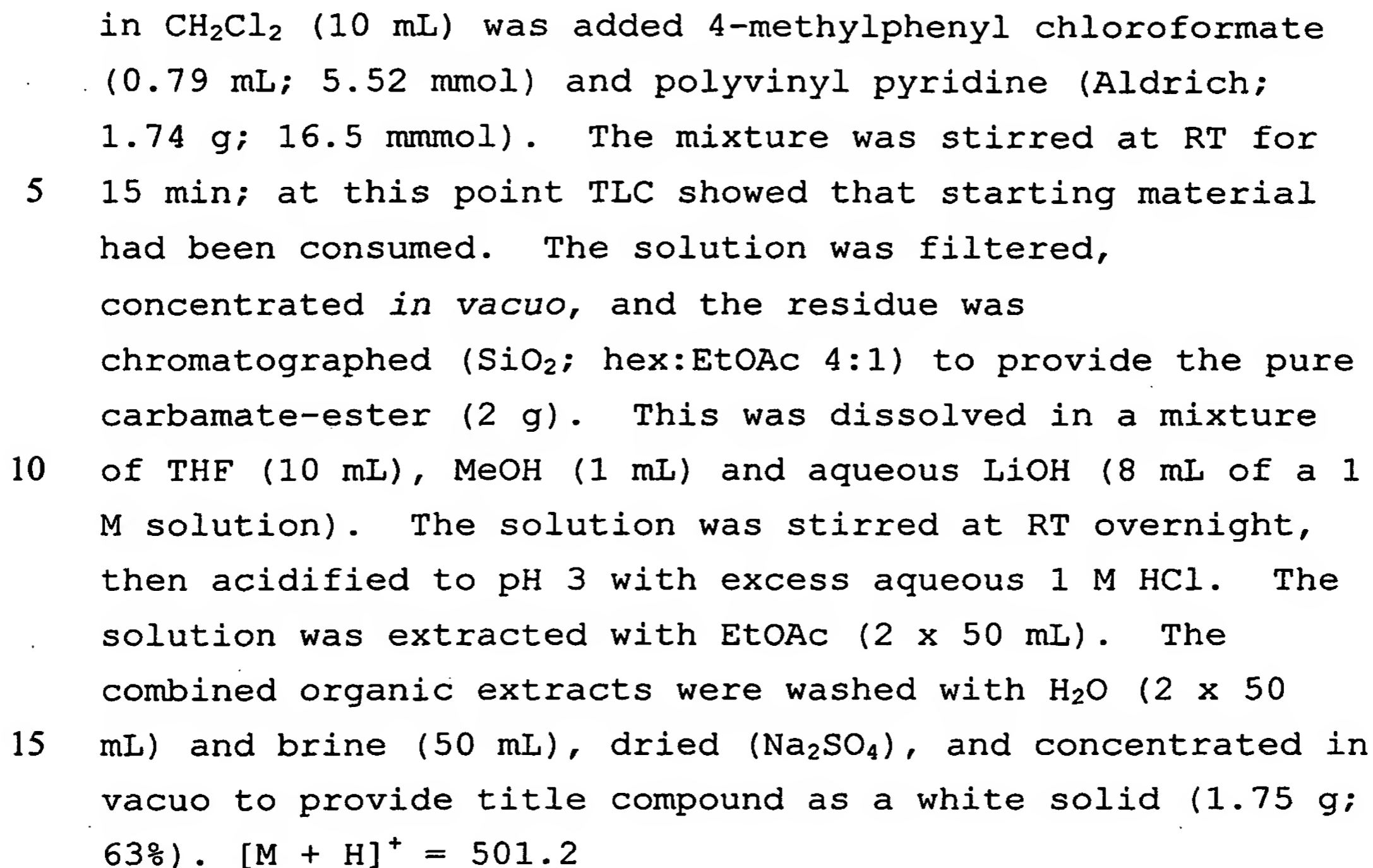
Example No.	R ^{3d}	[M+H] ⁺
286		515.3
287		535.2
288		529.2
289		577.3
290		515.2
291		529.2
292		527.3
293		537.3
294		531.3
295		555.2
296		571.3
297		573.2



Example 149



To a solution of the secondary amine-ester (2.1 g;
5.52 mmol)

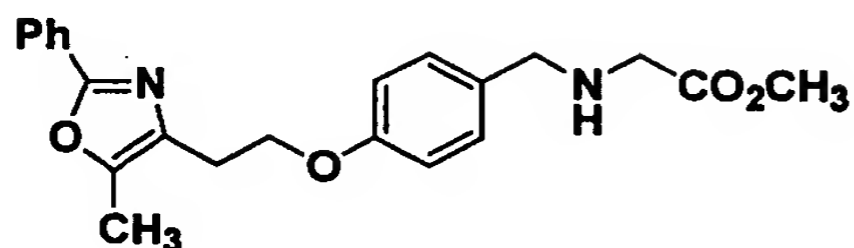


20 $[M + H]^+ = 501.2$; 1H NMR (400 MHz; $CDCl_3$): δ 7.93-7.99 (m, 2H), 7.38-7.43 (m, 3H), 7.23 (q, 1H, $J = 8$ Hz), 7.02-7.12 (m, 3H), 6.98-7.02 (m, 2H), 6.82-6.89 (m, 2H), 4.71 (s, 1H), 4.64 (s, 1H), 4.25 (t, 2H, $J = 7$ Hz), 4.07 (s, 2H), 2.90-2.98 (m, 2H), 2.37 (s, 3H), 2.29 (s, 3H)

Example 230



To a 0°C solution of the secondary amine (3.0 g; 7.9 mmol)



in CH₂Cl₂ (45 mL) were successively added pyridine (0.8 mL; 9.9 mmol) and 4-methoxyphenyl chloroformate (1.3 mL; 8.7 mmol). The reaction was stirred at 0°C for 3 h, at which point starting material had been consumed (by analytical HPLC). The reaction solution was washed with aqueous HCl (2 x 25 mL of a 1 M solution), brine (2x), dried (Na₂SO₄), and concentrated *in vacuo*. The crude product was chromatographed (SiO₂; stepwise gradient from 4:1 to 3:7 hex:EtOAc) to provide the desired carbamate-ester (4.2 g; 100%). The ester was dissolved in THF:MeOH:H₂O (50 mL of a 3:1:1 solution) and LiOH.H₂O (0.5 g; 11.9 mmol) was added. The solution was stirred overnight at RT. Starting material was still present by HPLC. More LiOH.H₂O (0.2 g; 4.8 mmol) was added and the mixture was briefly heated to solubilize the LiOH, then stirred at RT for 4 h. The reaction was complete at this point, and the mixture was acidified to pH 3 with excess aqueous 1 M HCl, then organic solvents were removed in *vacuo*. The residual aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were successively washed with H₂O and brine (50 mL each), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give title compound as a colorless solid (3.07 g; 75%).

[M + H]⁺ = 517.2; ¹H NMR (400 MHz; CDCl₃): δ 7.96-7.98 (m, 2H), 7.4-7.45 (m, 3H), 7.2-7.3 (m, 2H), 7.0-7.1 (m, 2H), 6.8-7.0 (m, 4 H), 4.65 (s, 1H), 4.55 (s, 1H), 4.20-4.24 (m, 2H), 4.02 (s, 2H), 3.77 (s, 3H), 3.00 (s, 2H), 2.38 (s, 3H).

5

COc1ccc(OC(=O)NCCN(Cc2ccc(OCCc3c(C)c(O)c(C4=CC=CC=C4)N3)c2)cc1)cc1

15

CC1=C(CCOc2ccc(cc2)CN(C)C(=O)O)C(=O)c3ccccc3N1C(=O)Oc4ccccc4Br

25

CC1=C(C(=C(C=C1)OCC2=CC=CC=C2C(=O)NCC(=O)O)COC3=CC=C(C=C3)COC4=CC=CC=C4C5=CC=CC=C5N2)C=C(C=C3)C(=N3C=CC=C3)O5

5

10

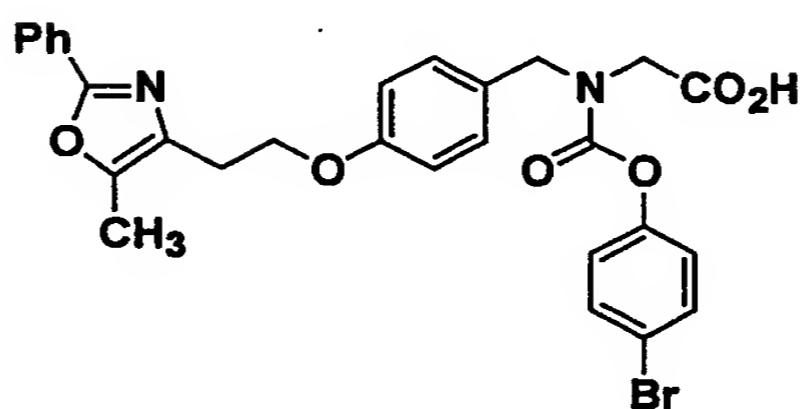


15

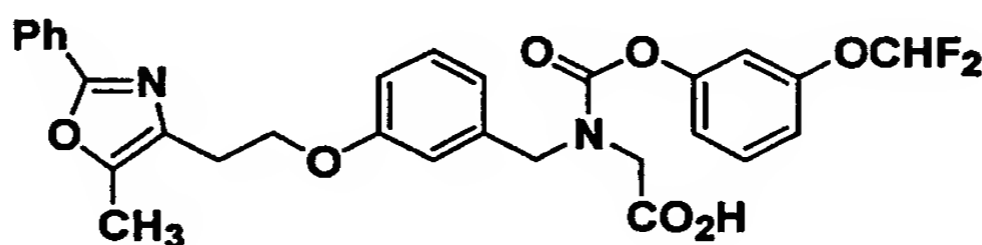
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25

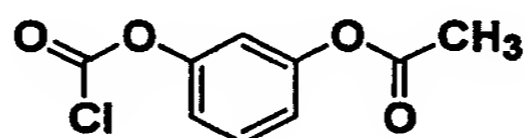
Example 263

5 ^1H NMR (CDCl_3 ; 400 MHz): δ 2.42 (2s, 3H; rotamers); 3.0-
 3.5 (m, 2 H), 3.99 (br s, 2 H), 4.15-4.25 (m, 2 H), 4.57
 (AB doublet, $J = 38.2$ Hz, 2 H), 6.85 (dd, $J = 11.4$, 8.8
 Hz, 2H), 6.99 (dd, $J = 15.8$, 8.8 Hz, 2H), 7.18 (dd, $J =$
 8.4, 2.6 Hz, 2H), 7.38-7.50 (m, 5H), 7.99 (br d, $J = 7.9$
 10 Hz, 2H)

Example 306

15

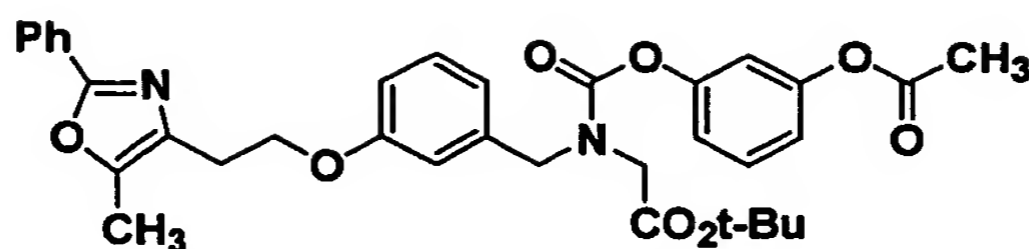
A.



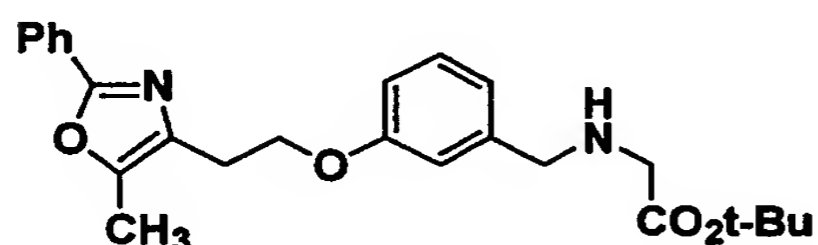
20 A solution of resorcinol monoacetate (2g; 13.14
 mmol), N,N-dimethylaniline (1.6g; 13.14 mmol), phosgene
 (6.8 mL of a 1.95M solution in toluene; 13.1 mmol) and a
 catalytic amount of DMF in chlorobenzene (5 mL) was
 heated at 80°C in a pressure tube for 2.5 h and then
 25 allowed to cool to RT. The clear supernatant solution
 was separated and concentrated *in vacuo*. The residue was
 purified via distillation *in vacuo* (140-150°C @ 1.0 mm
 Hg) to give title compound in the form of a clear oil (2
 g; 71%).

30

B.



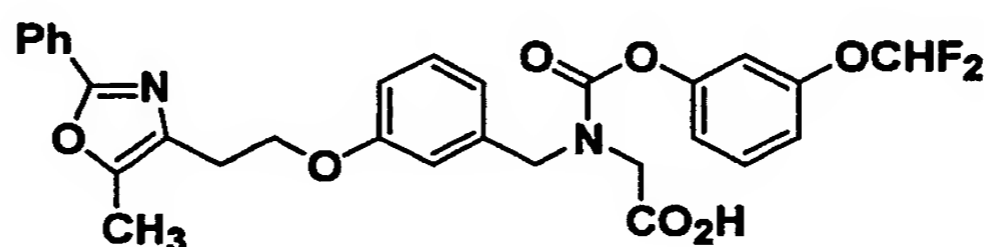
- 5 To a mixture of Part A chloroformate (50 mg, 0.237 mmol) and polyvinylpyridine (PVP) (75 mg, 0.70 mmol) was added a CH₂Cl₂ solution (2 mL) of the amino-tert-butyl ester (100 mg, 0.237 mmol),



- 10 (prepared as described in Example 7 Part B).

The reaction was stirred at RT for 15 min. Resin-bound amine (WA21J, Supelco; 150 mg) was added to the mixture. The reaction mixture was stirred for another 15 min. The Resin-bound amine and PVP were removed via
 15 filtration and the filtrate was concentrated *in vacuo* to give the crude product. The crude product was chromatographed (SiO₂; hexane/EtOAc 1:4) to provide title compound (0.1 g, 70%).

20 C.



A solution of the Part B phenol-tert butyl ester
 25 compound (60 mg; 0.10 mmol), Bu₄NBr (0.32 mg, 0.001 mmol), aqueous NaOH (0.5 mL of a 1 M solution; 0.5 mmol) and isopropanol (1 mL) in a pressure tube was cooled to -50°C. Freon gas was bubbled into the solution for 1 min. The tube was sealed and heated to 80°C for 12 h.

5
10
15

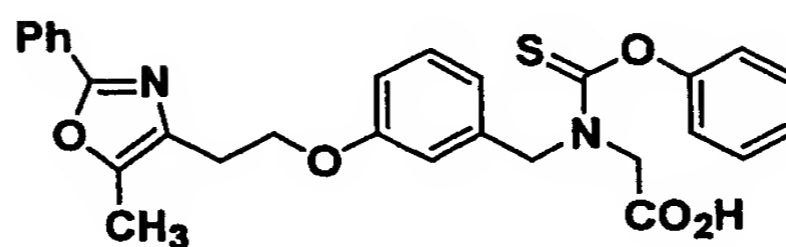


20

306, the following compounds were prepared:

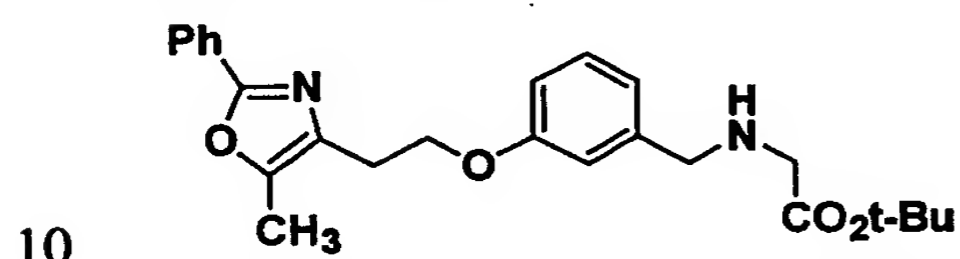


25

Example 309

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To a mixture of phenyl chlorothionoformate (11 mg, 0.063 mmol) and triethylamine (6.5 mg, 0.063 mmol) was added a solution of the amino-tert-butyl ester (20 mg, 0.053 mmol),



10

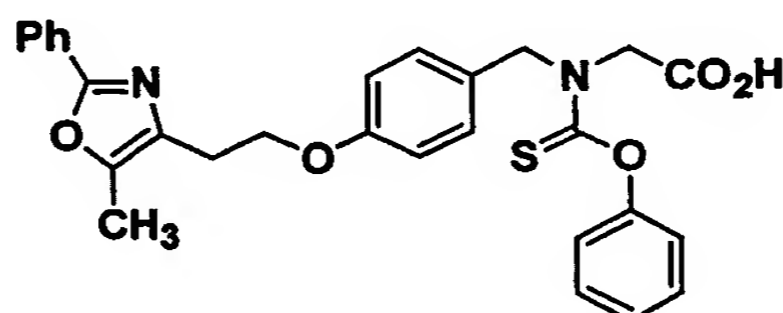
(prepared as described in Example 7 Part B) in CH_2Cl_2 (1 mL). The reaction was stirred at RT for 15 min and the mixture was concentrated *in vacuo* to give the crude thionocarbamate tert-butyl ester. This material was dissolved in aqueous LiOH (0.50 mL of a 1.0 M solution) and THF (2 mL) and stirred at RT for 5 h. The solution was concentrated *in vacuo* to give the crude acid as an oil. The crude product was purified using preparative HPLC to afford the desired title product (10 mg; 38%). $[\text{M} + \text{H}]^+ = 503.2$

20

Example 310

The corresponding thiocarbamate in the 1,4 series was prepared in the same manner as described for Example 309.

25



$[\text{M} + \text{H}]^+ = 503.2$

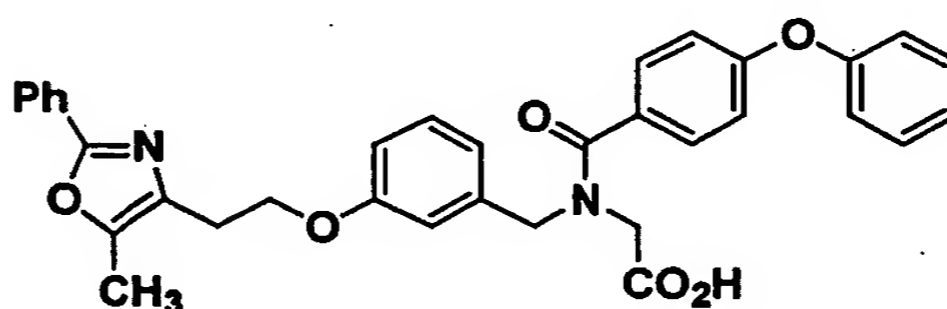
CC1=C(COP(=O)(OC(=O)NCC2=CC=CC=C2)C3=CC=CC=C3)OC(=N1)C4=CC=CC=C4CCOC(=O)CNCCc1ccc(OCCc2c(C)c(Oc3ccccc3n2)c4ccccc4)cc1

(prepared as described in Example 7 Part B), and p-phenoxybenzoic acid (220 mg; 1.02 mmol; 1.4 equiv) in CH₃CN (20 mL) was added BOP reagent (372 mg, 0.84 mmol, 1.15 equiv) in a single portion followed by iPr₂NEt (0.5 mL; 2.9 mmol; 3.9 equiv) dropwise. The reaction was stirred overnight at RT, after which volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and washed with aqueous 1N HCl. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with H₂O, sat'd aqueous NaHCO₃ and brine, dried (Na₂SO₄) and concentrated *in vacuo* to give the desired product. The resulting crude amide-ester was used in the next step without further purification.

A solution of the crude amide ester in 40% TFA-CH₂Cl₂ (25 mL) was stirred for 5h at RT. Volatiles were removed *in vacuo* and the crude acid was purified by Prep HPLC (YMC S5 ODS 30mm x 250 mm reverse phase column; flow rate = 25 mL/min; 30 min continuous gradient from 70:30 A:B to 100% B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA) to yield title compound (238 mg; 58% yield over 2 steps) as a white solid. Analytical Reverse-phase HPLC: Retention time = 7.53 min. (Continuous gradient solvent system: from 50% A:50% B to

0% A:100% B (A = 90% H₂O/10% MeOH/0.2% H₃PO₄; B = 90% MeOH/10% H₂O/0.2% H₃PO₄) for 8 min; detection at 220 nm; YMC S3 ODS 4.6 x 50 mm column). [M + H]⁺ = 563.3

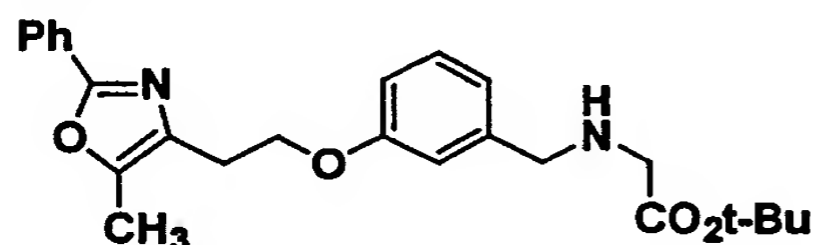
5

Example 311A

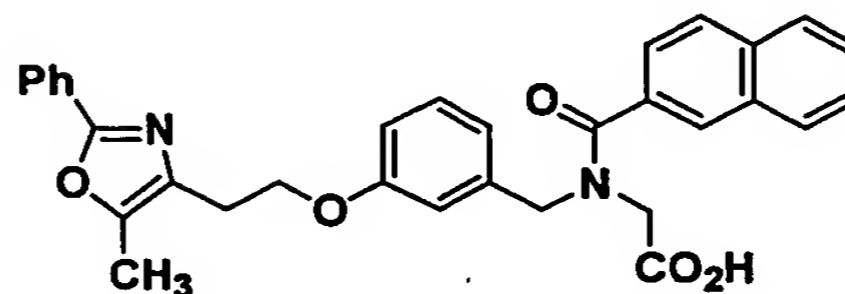
(alternative synthetic procedure)

10

To a solution of the secondary amine tert-butyl ester (35 mg, 0.083 mmol), (prepared as described in Example 7 Part B)

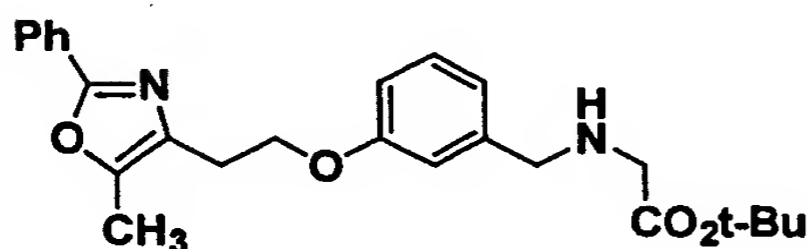


- 15 4-phenoxy benzoic acid (30 mg, 0.14 mmol) and HOAT (30 mg, 0.22 mmol) in THF/DMF (1 mL/0.05 mL) was added EDCI (20 mg, 0.10 mmol) and the mixture was stirred at RT overnight. The reaction was diluted with EtOAc, washed with aqueous 1N HCl, H₂O, sat'd. aqueous NaHCO₃ and
- 20 brine, dried (Na₂SO₄) and concentrated in vacuo. The crude amide-tert butyl ester was dissolved in TFA/CH₂Cl₂ (5 mL of a 1:1 solution). The resulting pink solution was stirred overnight and concentrated in vacuo to provide the crude acid-amide as a dark brown oil. The
- 25 crude product was purified by preparative HPLC (YMC S5 ODS 20 x 100 mm column, 10 min continuous gradient from 60:40 A:B to 100 % B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA; flow rate = 20 mL/min) to provide the title compound (32 mg, 69%).
- 30 [M + H]⁺ = 563.3

Example 312

5

- 1) To a solution of the secondary amine-tert-butyl ester (25 mg; 0.06 mmol)



- (prepared as described in Example 7 Part B),
10 in THF (0.5 mL) was added 2-naphthalene carboxylic acid (25 mg; 0.15 mmol; 2.5 equiv).

2) HOAT (48 mg; 0.35 mmol; 5.8 equiv) was added.

15 3) DMF (50 μ L) was added.

4) EDCI ((20 mg, 0.1 mmol, 1.8 m eq) was added.

5) The reaction vessel was shaken for 24 h at RT.

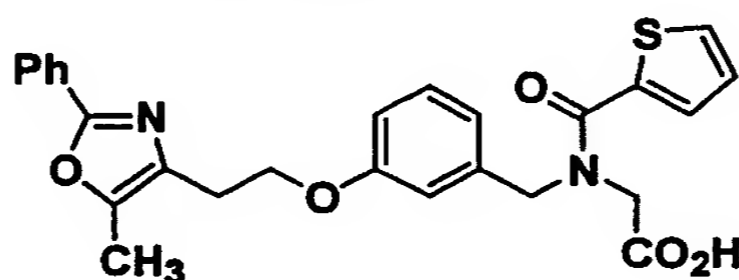
20

6) The reaction was diluted with MeOH (2 mL) and filtered.

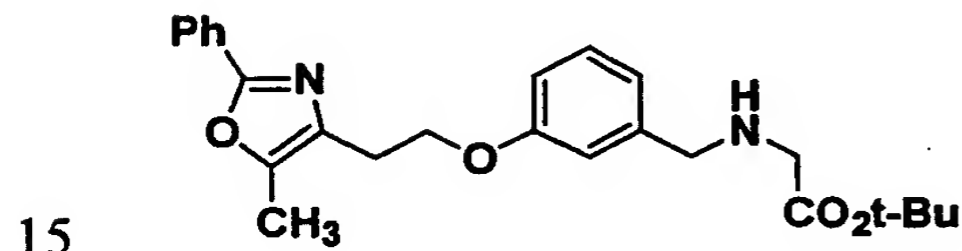
7) The amide-tert butyl ester was purified by preparative
25 HPLC (YMC S5 ODS 20 x 100 mm column; flow rate = 25 mL/min; 10 min continuous gradient from 70:30 A:B to 100% B; solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA).

8) The fractions containing the purified amide-ester were treated with a solution of TFA in CH_2Cl_2 (0.5 mL of a 1:1 solution) overnight. The reaction was concentrated in vacuo (Speed Vac) to give title compound (8 mg; 25%). Reverse-phase analytical HPLC showed that the purity of the product was > 88%; LC/MS (electrospray detection) gave the correct $[\text{M} + \text{H}]^+ = 521.2$ for the title compound.

10

Example 313

A mixture of the amino-ester (20 mg; 0.0474 mmol),



15

(prepared as described in Example 7 Part B),

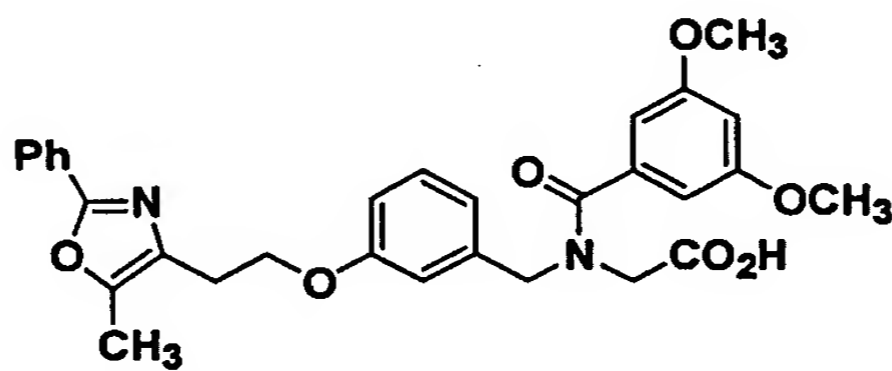
thiophene-2-carboxylic acid (9.1 mg, 0.71 mmol), EDCI (26 mg, 1.4 mmol) and DMAP (a catalytic amount) was dissolved in CH_2Cl_2 (2 mL) and stirred at RT overnight. The

20 reaction solution was successively washed with aqueous 1N HCl (2 mL) and sat'd aqueous NaHCO_3 (2 mL). To the organic phase was then added 0.5 g anhydrous Na_2SO_4 , and 0.2 g WA21J amine-bound resin (Supelco). The mixture was shaken for 0.5 h and the solids were filtered off. TFA
25 (2.0 mL) was added to the filtrate and the solution was shaken at RT overnight. The reaction solution was concentrated in vacuo using a Speed Vac for 16 h to afford title compound as a yellow oil. Reverse phase analytical HPLC (YMC S5 ODS 4.6 x 33 mm column,
30 continuous gradient from 100% A to 100%B for 2 min at a

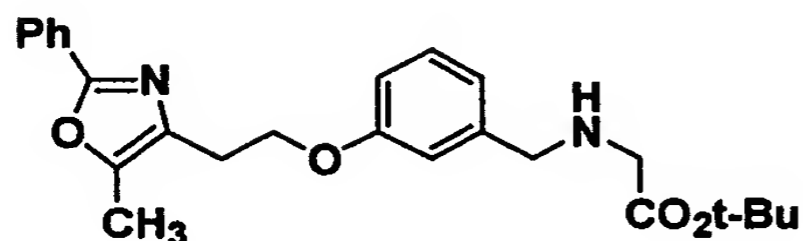
flow rate of 5 mL/min [Solvent A = 10% MeOH/90% H₂O/0.2% H₃PO₄; Solvent B = 90% MeOH/10% H₂O/0.2% H₃PO₄] indicated that the product purity was 92.7%. In addition, LC/MS (electrospray) gave the correct molecular ion [(M+H)⁺ = 477.2] for the desired title compound.

Example 314

Another purification protocol using amine-bound resin for the amide-acid product is illustrated by the following synthesis:



To a mixture of the amino-ester (20 mg; 0.0474 mmol),



(prepared as described in Example 7 Part B), and 3,5-dimethoxybenzoic acid (13 mg, 0.071 mmol) in anhydrous CH₃CN (0.5 mL) was added a solution of BOP reagent (31 mg, 0.071 mmol) in CH₃CN (0.5 mL), followed by DIEA (41 μL, 0.23 mmol) in CH₃CN (0.5 mL). The reaction was shaken at RT overnight. Volatiles were removed *in vacuo* using a Speed Vac and CH₂Cl₂ (2 mL) was added. The solution was washed successively with aqueous 1N HCl (2 mL) and sat'd aqueous NaHCO₃ (2 mL). To the organic phase was added 0.5 g anhydrous Na₂SO₄, and 0.2 g

WA21J amine-bound resin (Supelco). The mixture was shaken for 0.5 h and the solids were filtered. TFA (2 mL) was added to the filtrate and the solution was shaken at RT overnight. The reaction solution was concentrated in vacuo using a Speed Vac for 16 h to afford the final product as a yellow gum. Reverse-phase analytical HPLC (YMC S5 ODS 4.6 x 33 mm column, continuous gradient from 100% A to 100% B for 2 min at a flow rate of 5 mL/min [Solvent A = 10% MeOH/90% H₂O/0.2% H₃PO₄; Solvent B = 90% MeOH/10% H₂O/0.2% H₃PO₄]) indicated that the product purity was 90%. In addition, LC/MS (electrospray) gave the correct molecular ion $[(M+H)^+ = 531.3]$ for the title compound.

15

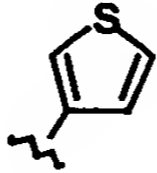
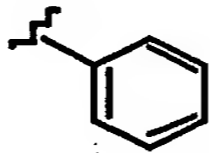
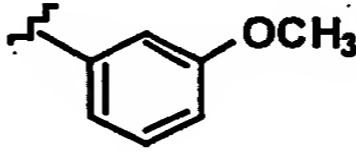
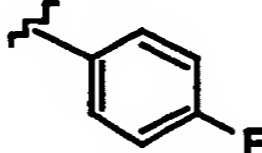
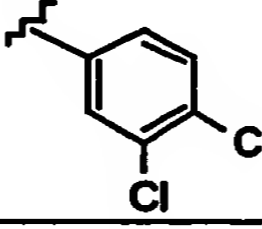
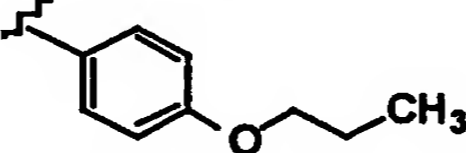
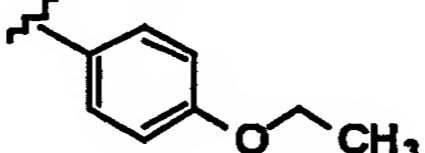
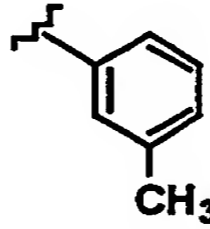
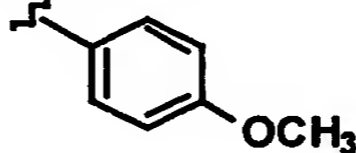
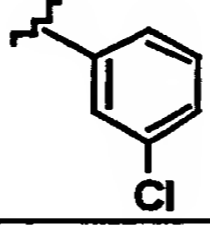
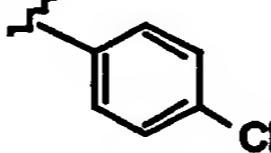
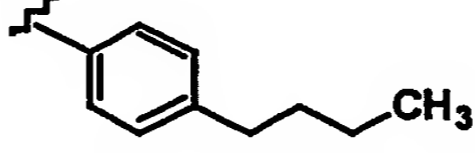
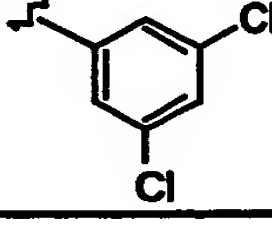
Examples 315 to 391

Following one of the above procedures, the following compounds in Tables 6 and 7 of the invention were prepared.

CC1=C(CCOc2ccc(cc2)CN(CCC(=O)O)C(=O)R3e)N(=C1C3)C4=CC=CC=C4

- 164 -

- 165 -

Example No.	R ^{3e}	[M+H] ⁺
337		477.2
338		471.2
339		501.3
340		489.2
341		539.2
342		529.3
343		515.3
344		485.3
345		501.3
346		505.2
347		505.2
348		527.3
349		539.2

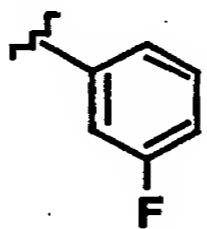
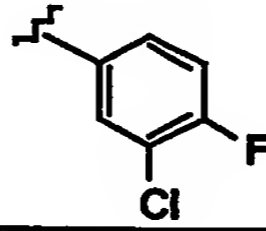
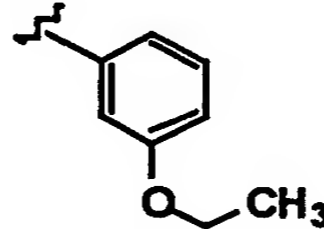
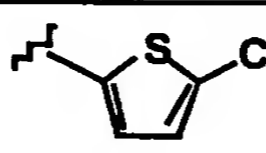
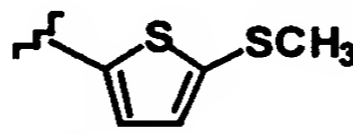
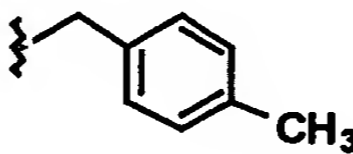
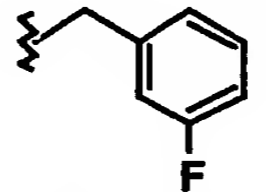
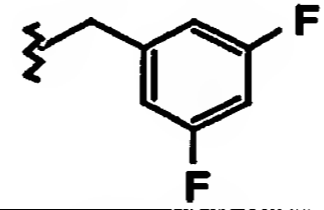
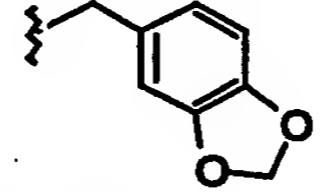
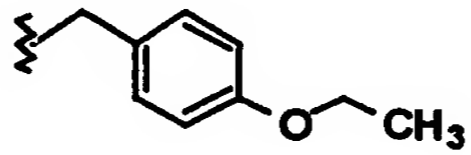
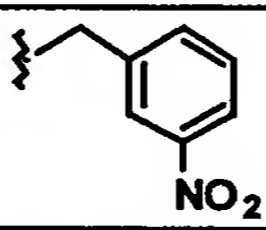
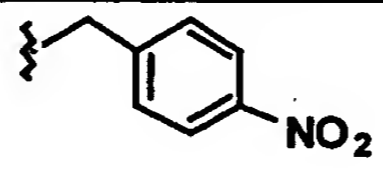
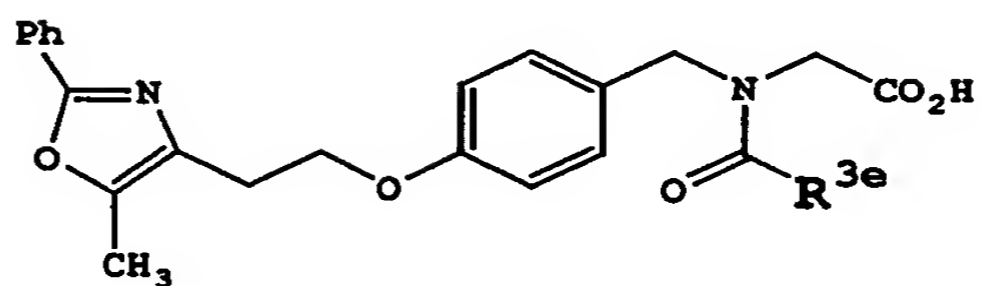
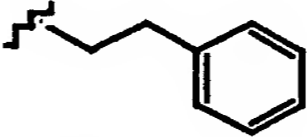
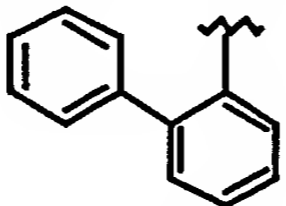
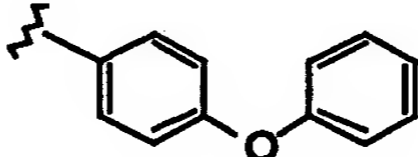
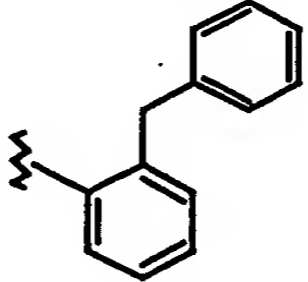
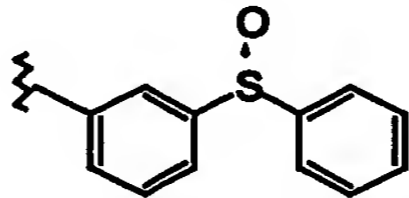
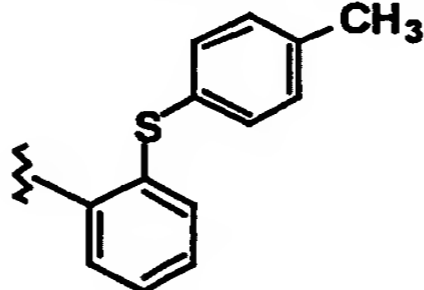
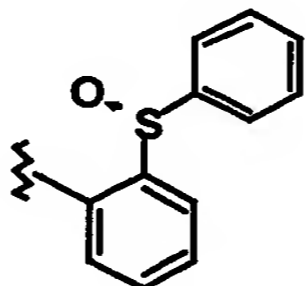
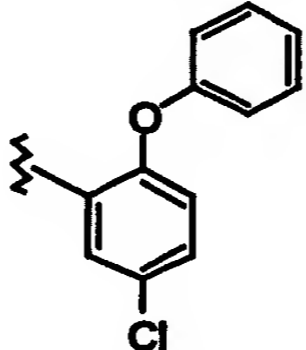
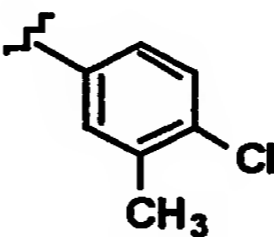
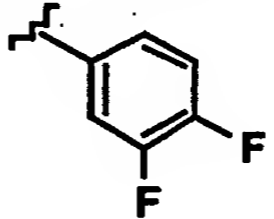
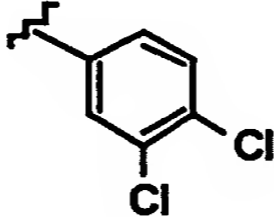
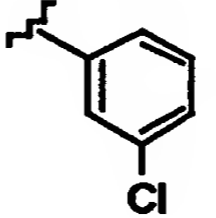
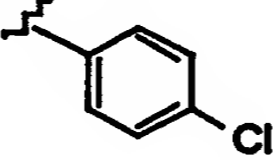
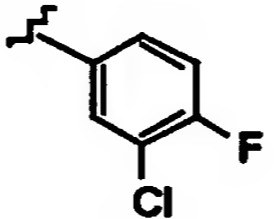
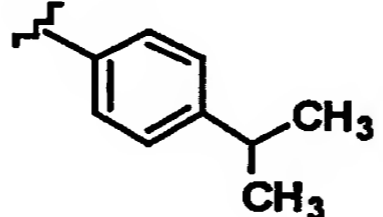
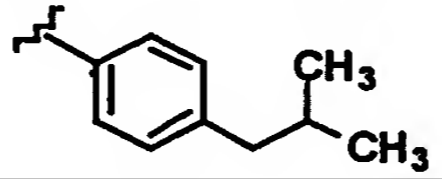
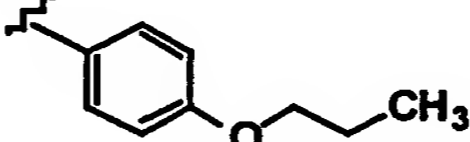
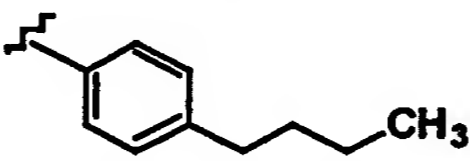
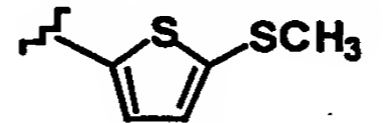
Example No.	R ^{3e}	[M+H] ⁺
350		489.3
351		523.2
352		515.3
353		511.2
354		523.1
355		499.2
356		503.2
357		521.2
358		529.2
359		529.2
360		530.2
361		530.2

Table 7: (Amide-Acids)

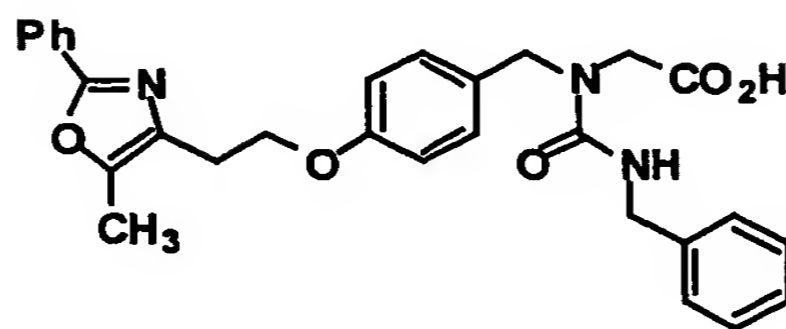


Example No.	R ³	[M+H] ⁺
362		499.2
363		547.2
364		563.2
365		561.1
366		595.1
367		593.1
368		595.1
369		597.1

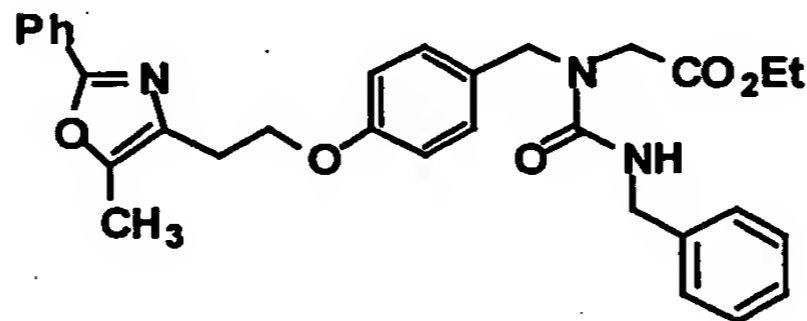
- 169 -

Example No.	R ³	[M+H] ⁺
381		519.3
382		507.3
383		539.2
384		505.2
385		505.2
386		522.7
387		513.3
388		527.3
389		529.3
390		527.3
391		523.1

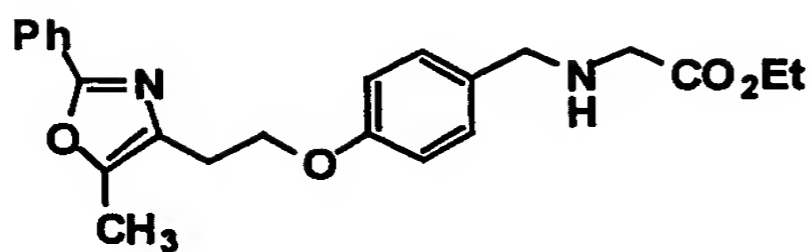
Example 392



A.

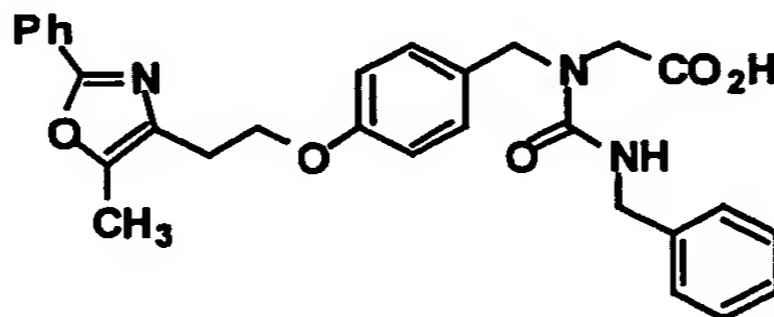


To a solution of the amine (47 mg; 0.12 mmol)



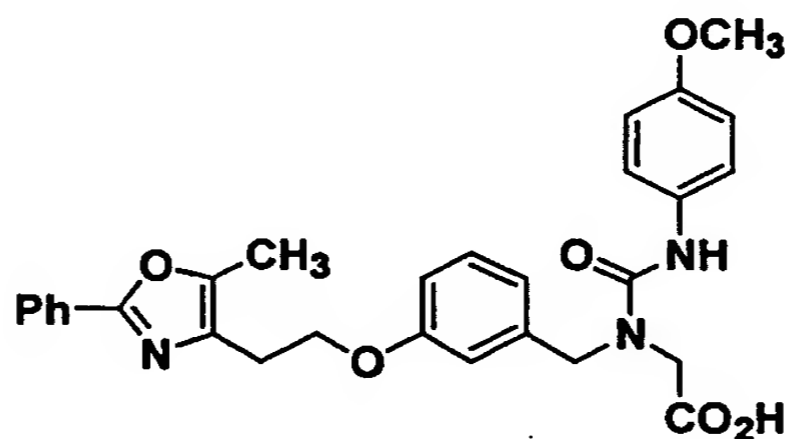
(prepared as described in Example 3 Part A),
in CH_2Cl_2 (5 mL) were added $i\text{Pr}_2\text{NEt}$ (0.1 mL; 0.57 mmol)
and DMAP (14 mg; 0.12 mmol) followed by benzyl isocyanate
(24 mg; 0.18 mmol). The reaction was stirred for 14h,
then passed through an SCX cartridge [the 3g SCX
cartridge was prewashed successively with MeOH (10 mL)
and CH_2Cl_2 (5 mL)] by eluting with CH_2Cl_2 (15 mL). The
filtrate was concentrated in vacuo to give the crude urea
Part A compound (53 mg; 84%), which was sufficiently pure
to be used in the next step without further purification.

B.

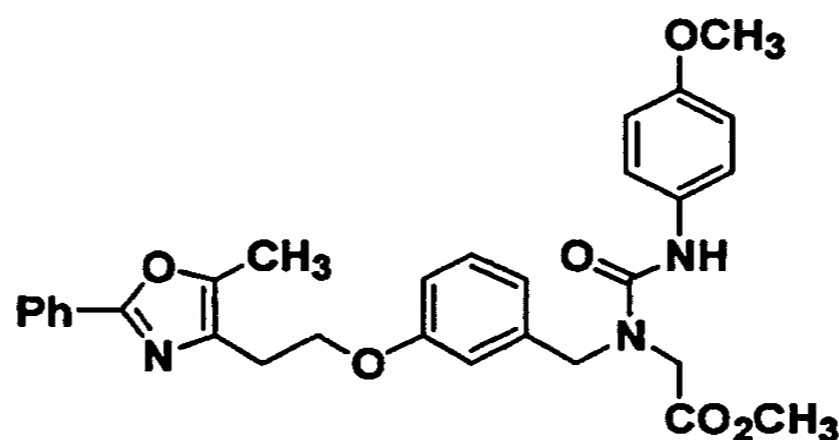


A solution of the crude Part A urea-ethyl ester (53 mg) and LiOH.H₂O (12 mg) in THF: MeOH:H₂O (3:1:1; 5 mL) was stirred at RT for 2 days. The solution was acidified to pH3 with aqueous 1M HCl, concentrated *in vacuo*, and purified by preparative HPLC (utilizing a YMC S5 ODS 20mm x 100 mm column; with a continuous gradient from 70%A:30%B to 100% B for 10 minutes at a flow rate of 20 mL/min, where A = 90:10:0.1 H₂O:MeOH:TFA and where B = 90:10:0.1 MeOH:H₂O:TFA) to give title compound (12 mg; 24%) as an off-white solid. [M + H]⁺ = 500.2

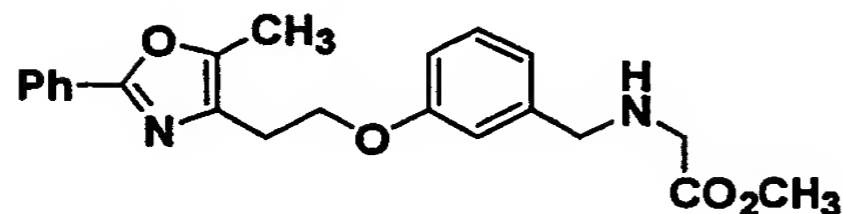
Example 393



15 A.



To a solution of the amine (0.25 g, 0.66 mmol)

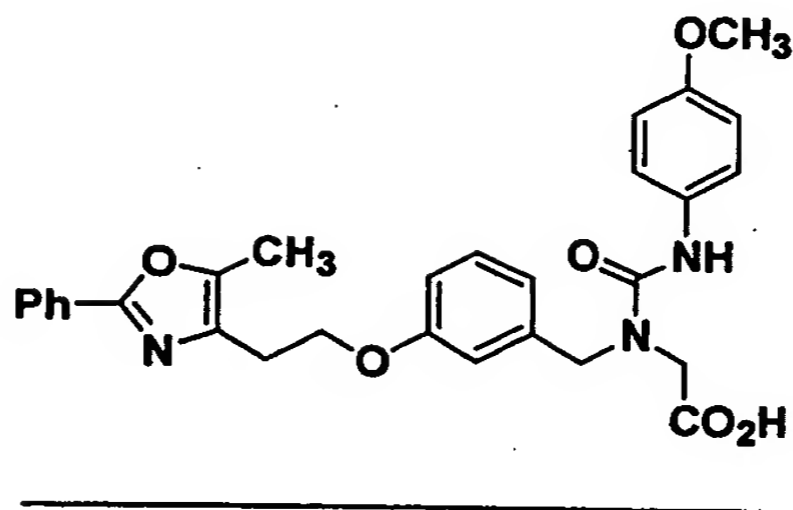


20

(prepared as described in Example 6), in CH₂Cl₂ (5 mL) was added 4-methoxyphenyl isocyanate (0.20 g, 1.32 mmol) in one portion and the resulting solution was stirred for 1 h at RT. The reaction mixture was then concentrated *in vacuo* to give an oil, which was

25

B.



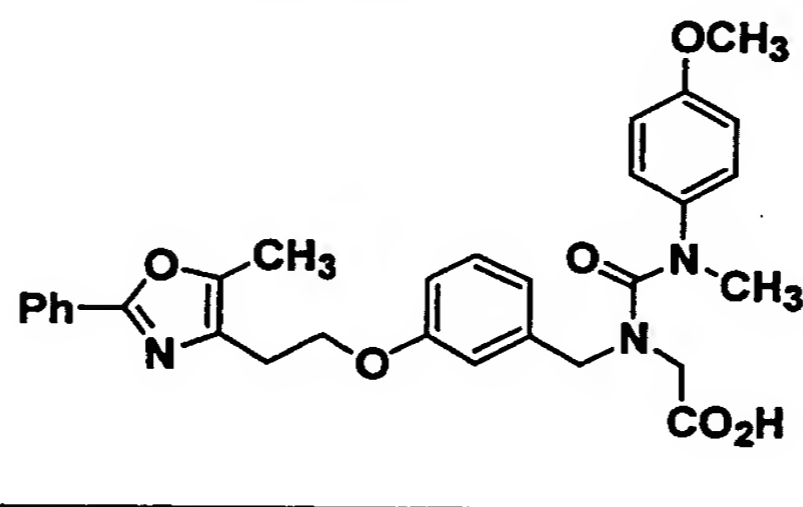
10 A solution of Part A compound (0.14 g, 0.26 mmol) and LiOH (0.1 g, 4.3 mmol) in H₂O/THF (5 ml of a 40:60 solution) was stirred for 12 h at 25°C. The reaction mixture was acidified with HOAc and extracted with EtOAc (2x). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to provide title compound (0.12 g; 90%) as a colorless oil. $[M + H]^+ = 516$

15

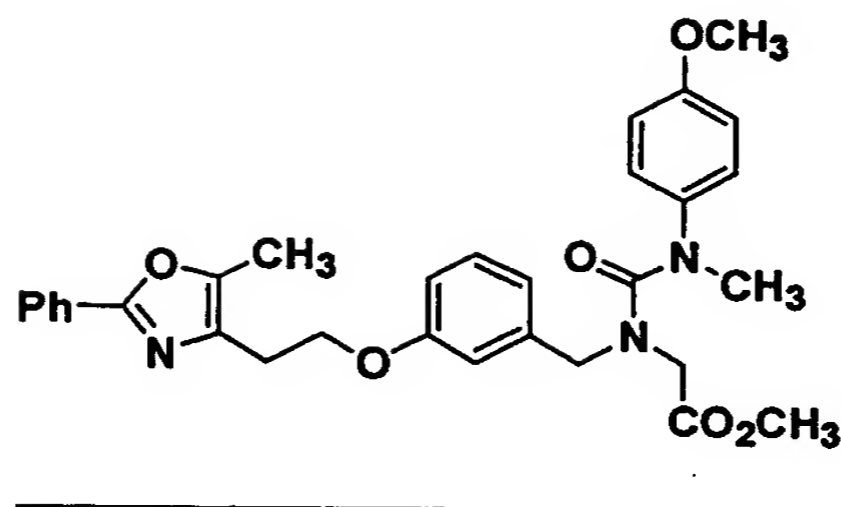
^1H NMR (CD_3OD ; δ): 7.94 (m, 2H), 7.45 (m, 3H), 7.23 (m, 3H), 6.80 (m, 2H), 6.80 (m, 3H), 4.58 (s, 2H), 4.23 (t, $J = 7.9$ Hz, 2H), 3.81 (s, 2H), 3.73 (s, 3H), 2.98 (t, $J = 7.9$ Hz, 2H), 2.36 (s, 3H).

20

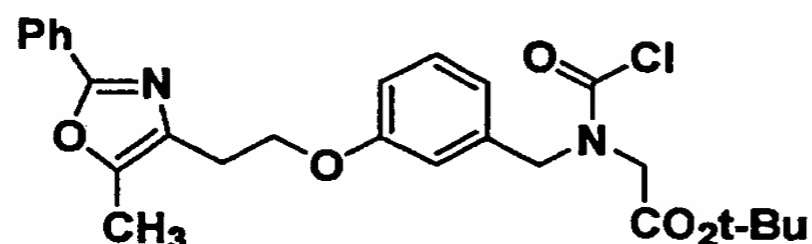
Example 394



A.

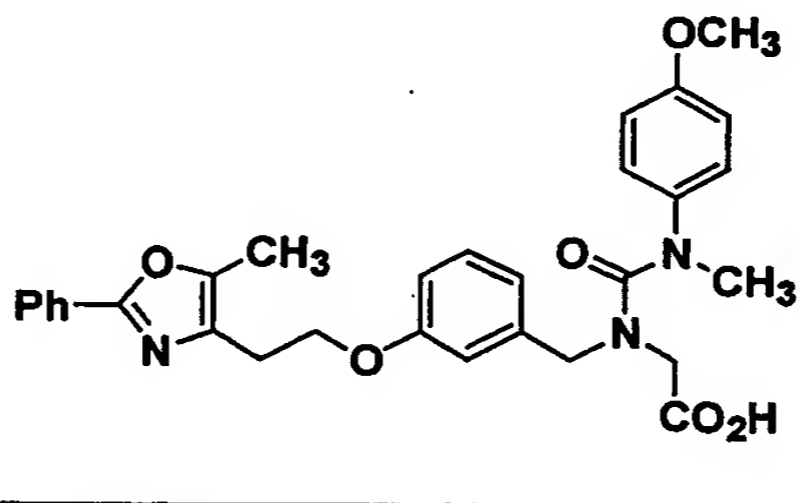


5 A solution of the previously described carbamoyl chloride (Example 139 Part A compound; 0.15 g; 0.34 mmol)



10 N-methyl-p-anisidine (0.14 g, 1.0 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) in 5 ml of acetone was stirred at 25 °C for 12 h. The reaction mixture was concentrated in vacuo to yield an oily residue, which was chromatographed (SiO_2 ; 1.5% MeOH/ CH_2Cl_2) to provide title compound (0.12 g; 65%) as a colorless oil.

15 B.



20 A solution of Part A compound (0.12 g, 0.22 mmol) and LiOH (0.050 g, 2.1 mmol) in H_2O/THF (5 mL of a 40:60 solution) was stirred at RT for 12 h. The reaction mixture was concentrated in vacuo to yield an oily residue, which was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 ml/min. 30 min continuous gradient from A:B = 50:50 to 100%B; solvent

25

A=90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1

MeOH:H₂O:TFA) to provide title compound (59 mg, 50%) as a colorless oil. $[M + H]^+ = 530.3$

- 5 NMR (CDCl₃): 7.99 (d, 6.2 Hz, 2H, 7.45 (m, 3H), 7.24 (m, 3H), 6.82 (d, 6.2 Hz, 2H), 6.79 (m, 1H), 6.63 (m, 1H), 6.55 (s, 1H), 4.24 (s, 2H), 4.16 (t, 7.8 Hz), 2H), 3.72 (s, 3H), 3.59 (s, 2H), 3.16 (s, 2H), 3.02 (t, 7.8 Hz, 2H), 2.40 (s, 3H).

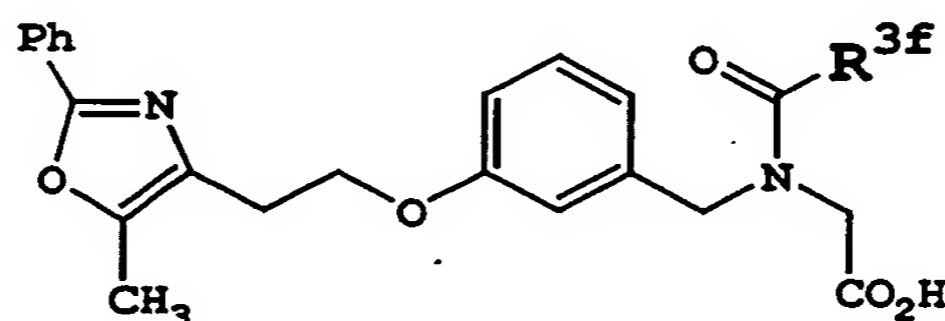
10

Examples 395 to 410

Utilizing one of the above procedures, the analogs in Tables 8 and 9 were synthesized.

15

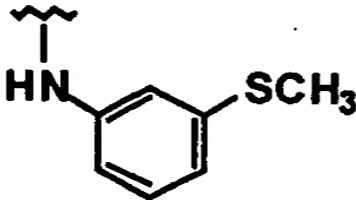
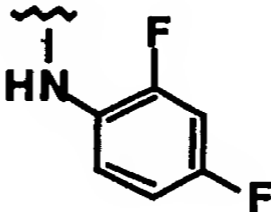
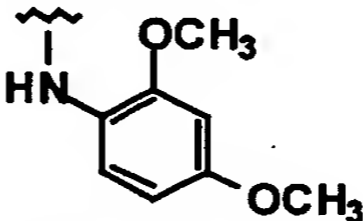
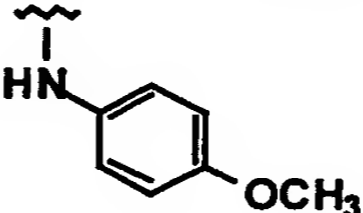
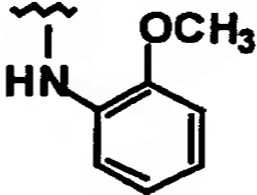
Table 8: (Urea-Acids)



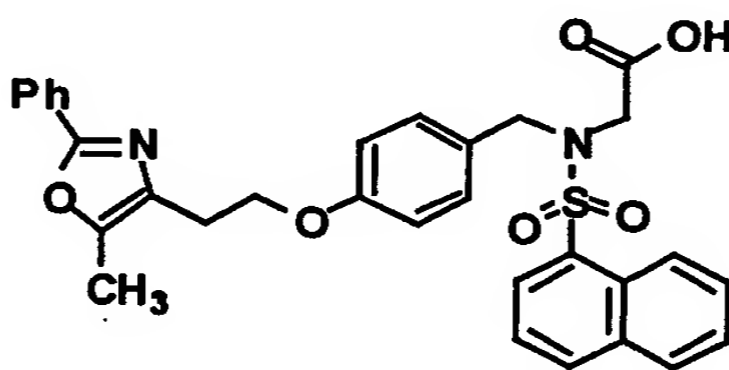
Example No.	R ^{3f}	[M+H] ⁺
395		562.3
396		546.3
397		554.2



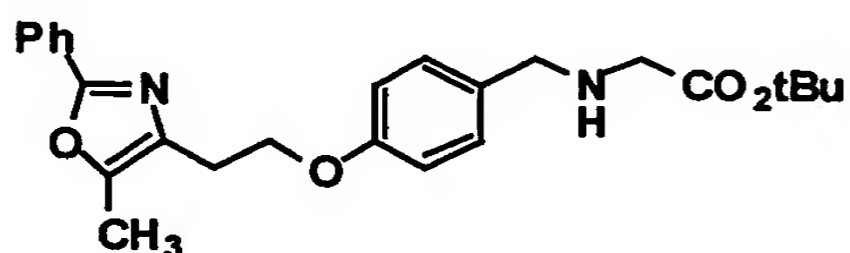
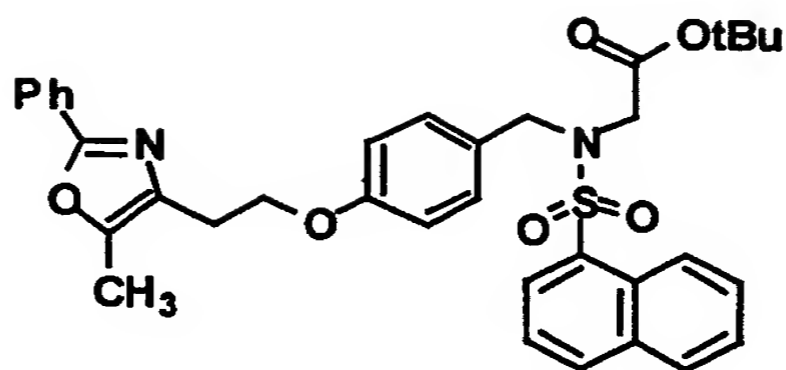
- 176 -

Example No.	R ^{3f}	[M+H] ⁺
405		532.3
406		522.3
407		546.3
408		516.3
409		516.3

Example 410



The title compound was prepared as part of a solution phase library run using the following procedure:



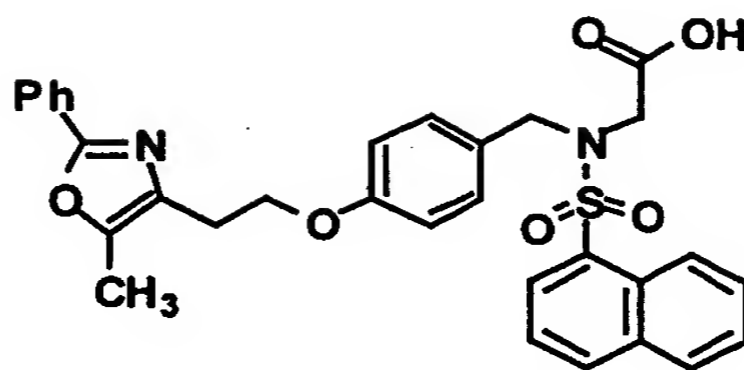
10 (20 mg, 0.05 mmol) in pyridine (0.6 mL). The reaction was stirred at RT for 20 h. Resin-bound amine (WA21J, Supelco; 5.8 mmol/g loading; 150 mg) was added to the mixture. The reaction was stirred for a further 4 h. The resin was filtered off and the filtrate was

15 concentrated *in vacuo* to give the crude product, which was chromatographed (CUSIL12M6 column; United technology; 2 g of sorbent in a 6 mL column) by the procedure outlined below.

2) The residue was dissolved in a minimal volume of EtOAc and loaded onto the silica gel column.

30

B.

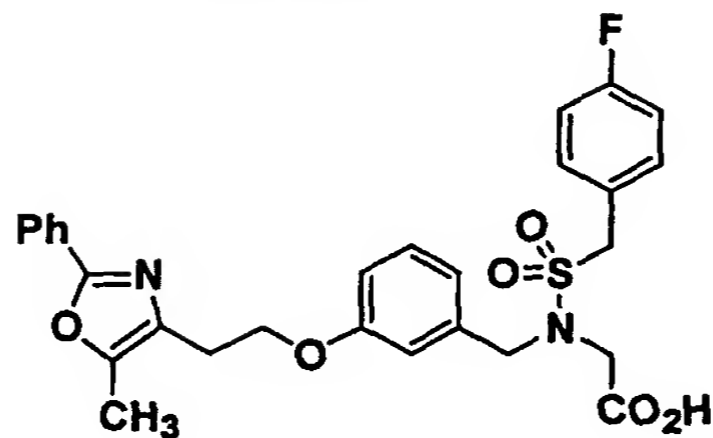


5 Et₃N ((0.3 ml of a 1M solution in CH₂Cl₂) and TMSI
(0.3 ml of a 1M solution in CH₂Cl₂) were successively
added to a solution of Part A compound in CH₂Cl₂. The
reaction mixture was stirred at RT for 12h and then was
concentrated *in vacuo* to give the crude product. The
10 product was purified by solid-phase extraction using a
CHQAX12M6 column (United technology; 2 g of sorbent in a
6 mL column) by the procedure outlined below.

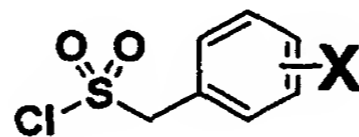
- 1) The column was conditioned with CH₂Cl₂ (25 mL).
15
2) The residue was dissolved in a minimal volume of CH₂Cl₂
and loaded onto the SAX column.
3) The cartridge was washed successively with CH₂Cl₂ (25
20 mL), CH₂Cl₂/MeOH (5% MeOH, 15 mL), CH₂Cl₂/MeOH (50% MeOH,
15 mL), MeOH (20 mL).
4) The product was eluted with a solution of 1% TFA in
MeOH (20 mL).

25

The final product-containing fraction was collected
and concentrated *in vacuo* using a Speed Vac to afford
BMS-329075 (16 mg; 62%). Reverse-phase analytical HPLC
indicated that the product purity was 90%. In addition,
30 LC/MS (electrospray) gave the correct molecular ion
[(M+H)⁺ = 557.1] for the desired compound.

Example 411

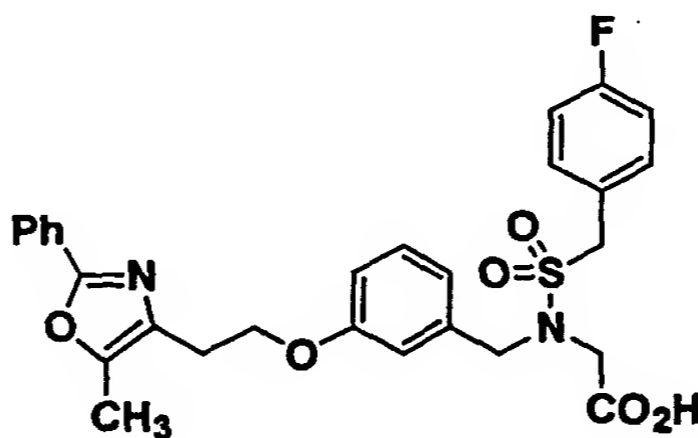
A.

(X = halogen, alkyl, CF₃, CF₃O, etc.)

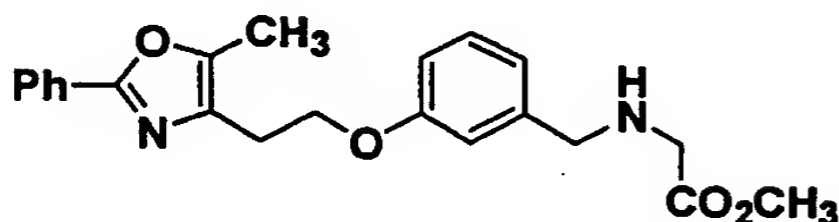
The following general procedure was utilized for the preparation of the requisite substituted benzyl sulfonyl chlorides:

Cl₂ gas was bubbled into a 0°C solution of 4-fluorobenzyl mercaptan (1.0 g, Lancaster) in glacial acetic acid (100 mL) and H₂O (5.0 mL) for 1h. The reaction mixture was then poured into ice-H₂O and immediately extracted with CH₂Cl₂ (200 mL); the organic phase was cautiously washed successively with H₂O (200 mL), aqueous saturated NaHCO₃ (2 x 100 mL), and finally brine (200 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo to furnish 4-fluorobenzyl sulfonyl chloride as a colorless solid (1.3 g; 89%).

B.



To a solution of the secondary amine methyl ester
(25 mg; 0.066 mmol)

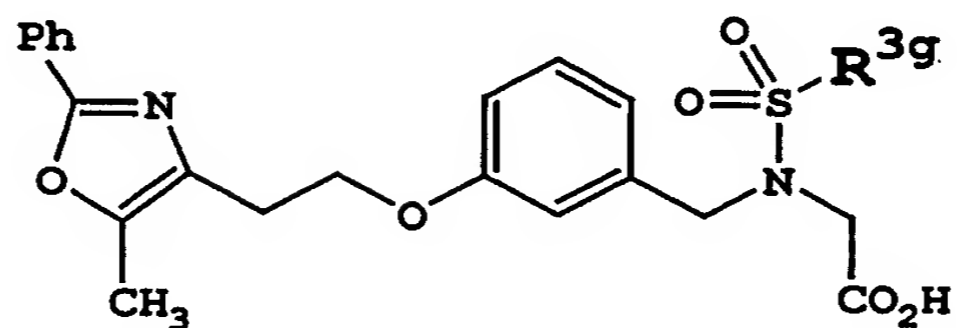


5 (prepared as described in Example 6),
in pyridine (0.8 mL) was added 4-fluorobenzyl sulfonyl
chloride (68 mg; 0.33 mmol; 5 equiv). The mixture was
heated to 75°C, stirred overnight at 75°C, and then
concentrated in vacuo. The black residue was treated
10 with aqueous LiOH (1.0 mL of a 0.3 M solution) in
H₂O/MeOH/THF for 18 h, then concentrated in vacuo. The
residue was acidified with 1.0 M aqueous HCl to pH = 1-2
and extracted with EtOAc (2x), dried (Na₂SO₄) and
concentrated in vacuo to give the crude product.
15 Purification by preparative HPLC (YMC S5 ODS 20mm x 250
mm reverse-phase column; 15 min continuous gradient from
60:40 A:B to 100% B with 10 min hold time, where A =
90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA;
flow rate = 25 mL/min) gave the title compound (12 mg;
20 34%) as a white solid. [M + H]⁺ (LC/MS) = 539.1

Examples 412 to 456

Utilizing one of the above procedures, the analogs in Tables 10 and 11 were synthesized.

Table 10: (Sulfonamide-Acids)



Example No.	R ^{3g}	[M+H] ⁺
412		507.3
413		575.2
414		525.2
415		521.2
416		533.2
417		513.2
418		535.3
419		575.2
420		581.1
421		590.3
422		589.2

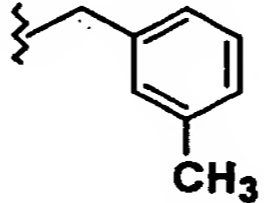
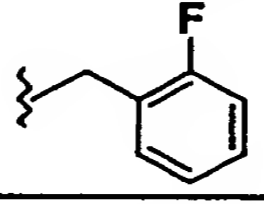
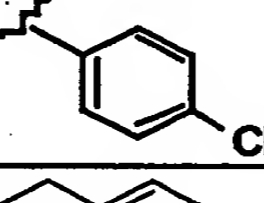
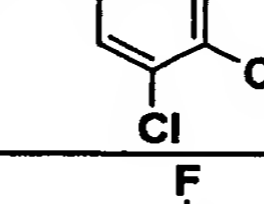
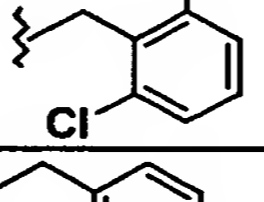
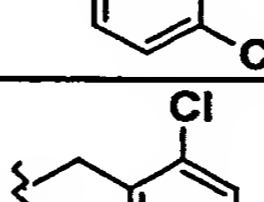
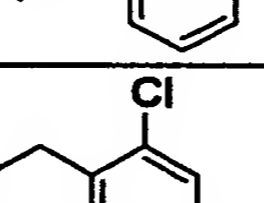
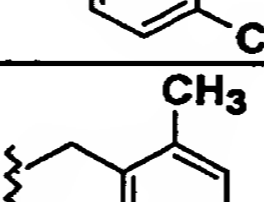
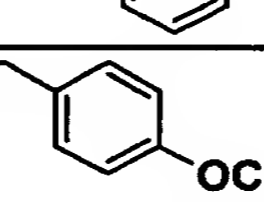
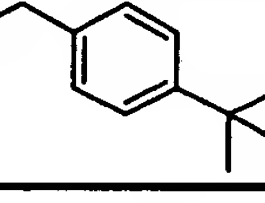

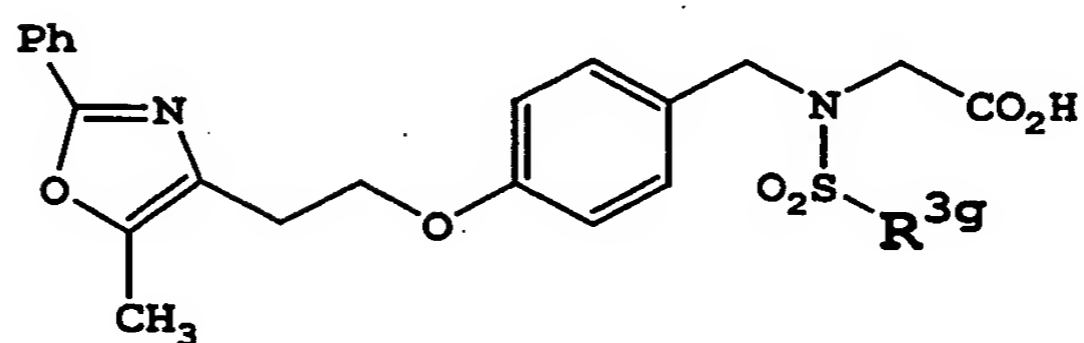
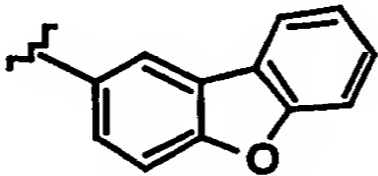
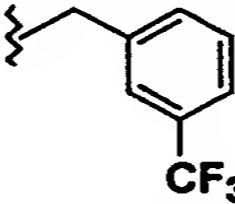
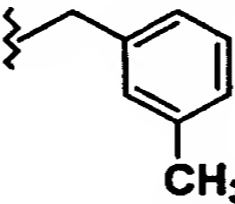
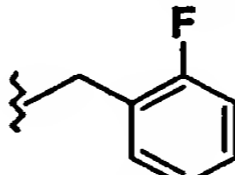
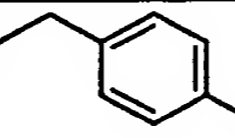
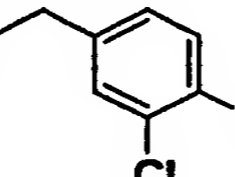
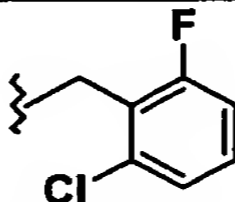
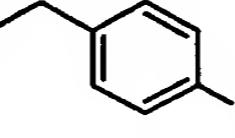
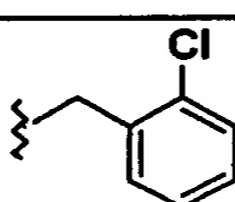
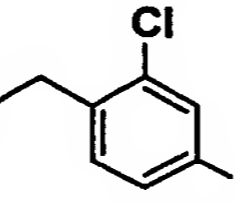
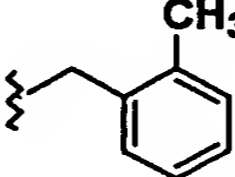
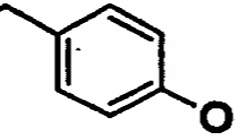
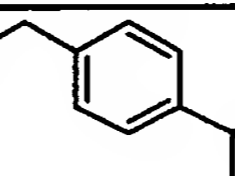
Example No.	R ^{3g}	[M+H] ⁺
423		535.3
424		539.1
425		541.2
426		589.0
427		573.2
428		555.2
429		555.3
430		589.2
431		535.3
432		605.3
433		577.4

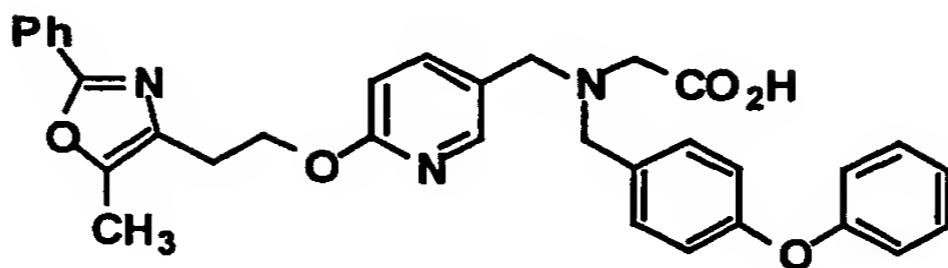
Table 11: (Sulfonamide-Acids)



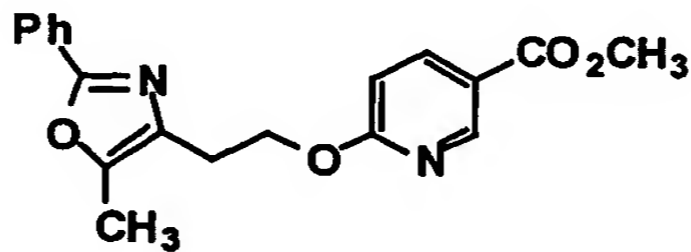
Example No.	R ^{3g}	[M+H] ⁺
434		549.4
435		557.3
436		506.3
437		549.3
438		541.2
439		521.3
440		533.3
441		535.4
442		575.3
443		678.3

Example No.	R ^{3g}	[M+H] ⁺
444		597.4
445		589.2
446		535.3
447		539.1
448		539.1
449		589.0
450		573.2
451		555.2
452		555.3
453		589.2
454		535.3
455		605.3
456		577.4

Example 457



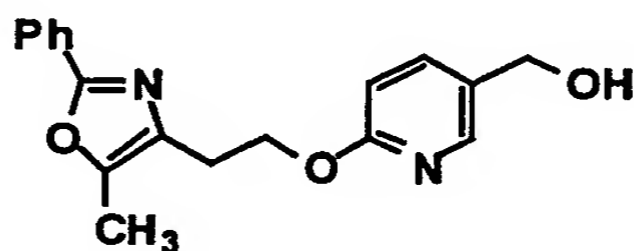
A.



5

15

B.

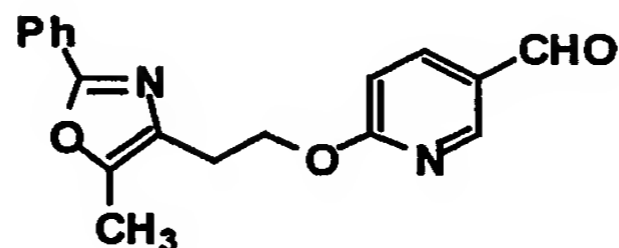


20

30

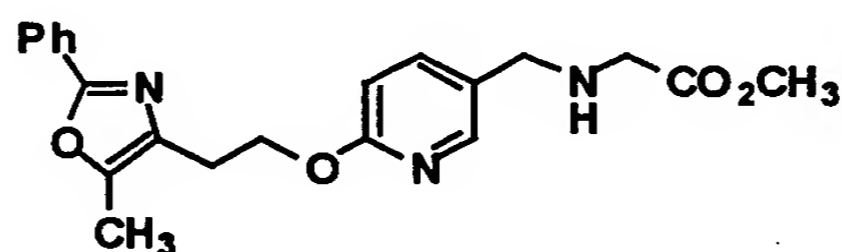
vacuo to furnish title compound as an oil. This crude material was used in the next reaction without further purification.

5 C.



To a -78°C solution of oxalyl chloride (0.22 mL, 2.6 mmol) and DMSO (0.37 mL, 5.2 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of Part B compound (0.42 g of crude material in 5 mL CH_2Cl_2). The reaction mixture was stirred for 2 h at -78°C and then Et_3N (1 mL) was added dropwise. The reaction mixture was stirred for an additional 0.5 h at -78°C and then was slowly warmed to 25°C . The reaction mixture was diluted with EtOAc (200 mL) and washed successively with aqueous NaHCO_3 and brine. The organic layer was dried (MgSO_4), then concentrated in vacuo to provide title compound (0.40 g; 95%) as an oil, which was used in the next step without further purification.

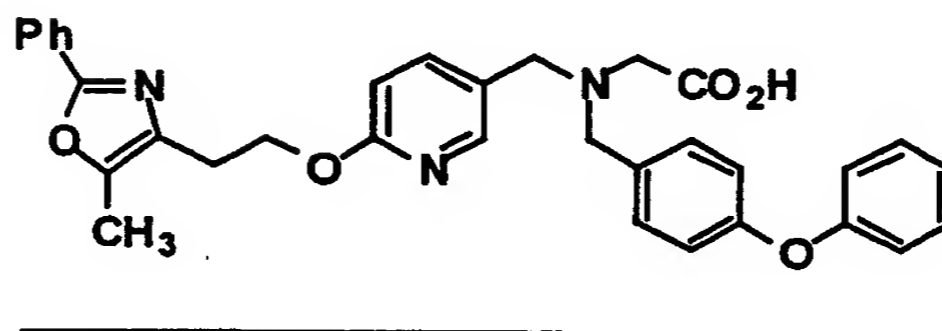
D.



25

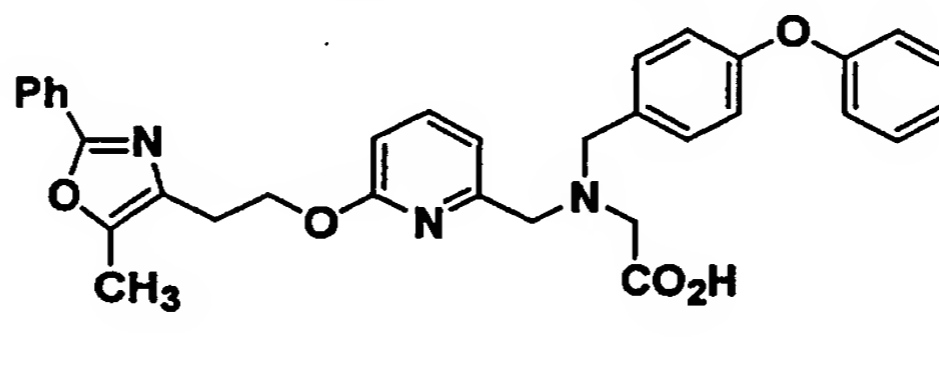
A mixture of Part C compound (<0.82 mmol), glycine methyl ester hydrochloride (0.5g., 4.0 mmol), $\text{NaBH}(\text{OAc})_3$ (0.85g., 4.0 mmol) and DCE (10 mL) was stirred at 25°C for 12 h. The reaction mixture was then diluted with EtOAc (50 mL) and washed successively with aqueous NaHCO_3 and brine. The organic layer was dried (MgSO_4), then concentrated in vacuo to give title compound (0.31 g;

5 E.



25 ^1H NMR (CDCl_3) δ : 8.18 (s, 1H), 7.94 (d, 6.6 Hz, 2H), 7.86 (d, 8.8 Hz, 1H), 7.45 (m, 3H), 7.34 (m, 3H), 7.14 (t, 7.4 Hz, 1H), 7.02-6.92 (m, 5H), 6.81 (t, 8.8 Hz, 1H), 4.51 (m, 6H), 3.59 (s, 2H), 3.06 (t, 6.2 Hz, 2H)

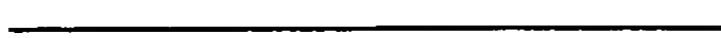
30 Example 458





10

15



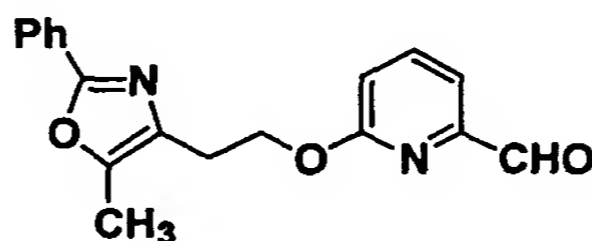
20

C.



To a solution of Part B compound (0.92 g, 2.7 mmol) in THF (50 mL) was added LiAlH₄ (5 mL of a 1.0 M solution in THF, 5 mmol) dropwise at -78°C and the resulting reaction was allowed to warm to 0°C over 2 h. The
5 reaction was then quenched by adding a few pieces of ice into the mixture. The reaction mixture was partitioned between EtOAc (200 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo to give an oil (0.92 g; 95%) which was used in the next reaction
10 without further purification.

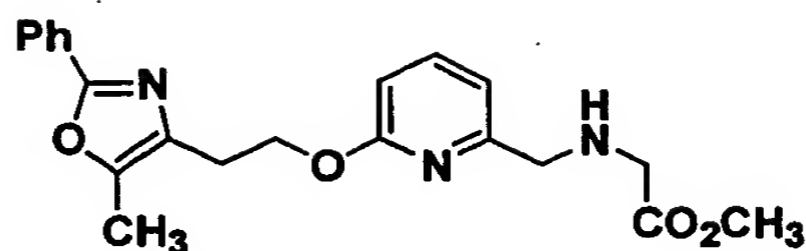
D.



15

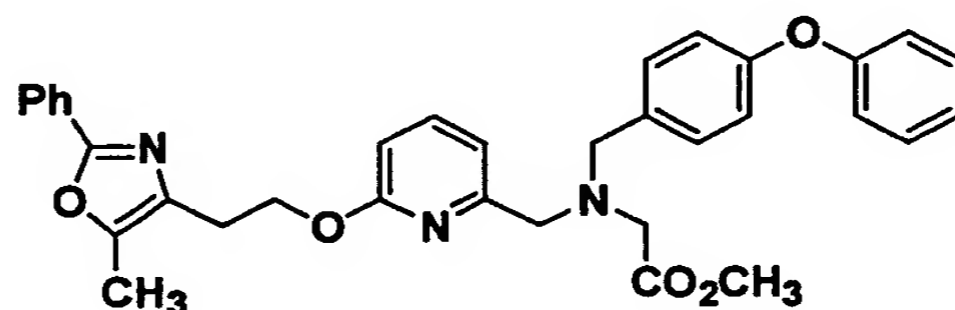
To a solution of oxalyl chloride (0.47 mL, 5.4 mmol) and DMSO (0.36 mL, 10.8 mmol) in CH₂Cl₂ (15 mL) was added dropwise a solution of Part C compound (0.92 g; >2.7 mmol) in CH₂Cl₂ (10 mL) at -78°C. The reaction mixture
20 was stirred for 2 h and then Et₃N (1 mL) was added dropwise. The reaction mixture was allowed to stir for an additional 0.5 h at -78°C and then slowly warmed to 25°C. The reaction mixture was then diluted with EtOAc (200 mL) and washed successively with aqueous NaHCO₃ and
25 brine. The organic layer was dried (MgSO₄) and then concentrated in vacuo to yield title compound (0.90 g; >90% pure by ¹H NMR analysis) as an oil. This material was used in the next step without further purification.

E.



5 To a solution of Part D compound (0.90g; 2.7 mmol),
glycine methyl ester hydrochloride (1.7 g, 13.5 mmol) in
1,2 dichloroethane (10 mL) was added $\text{NaBH}(\text{OAc})_3$ (1.7 g,
8.1 mmol) in one portion. The resulting solution was
10 stirred at 25°C for 12 h. The reaction mixture was
concentrated in vacuo to give an oil, which was
chromatographed (SiO_2 ; 30% acetone in hexane) to provide
title compound (0.86 g; 83%) as a colorless oil.

F.

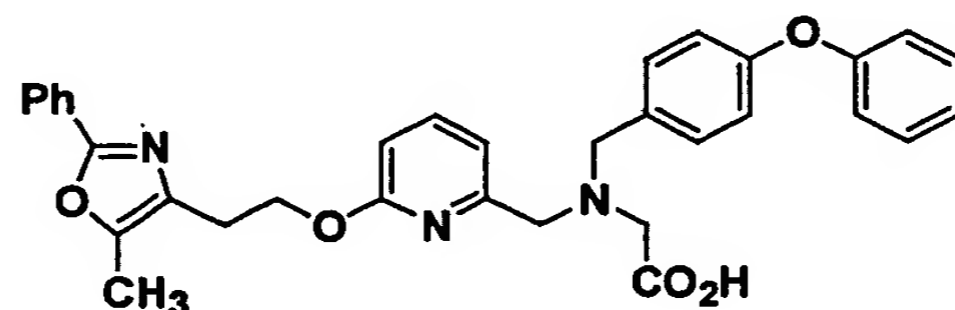


15

A solution of Part E compound (0.040 g, 0.1 mmol),
4-phenoxybenzaldehyde (0.030 g, 0.15 mmol) and $\text{NaBH}(\text{OAc})_3$
20 (0.060 g, 0.3 mmol) in DCE (10 mL) was stirred at RT for
12 h. The reaction mixture was concentrated in vacuo and
the oily residue was chromatographed (SiO_2 ; 30% acetone
in hexane) to provide the amino-ester title compound (56
mg; >95%) as a colorless oil.

25

G.



¹H NMR (MeOH-D₄): 7.90 (m, 2H), 7.71 (t, 8.4 Hz, 1H), 7.51 (d, 8.7 Hz, 2H), 7.44 (m, 3H), 7.36 (t, 8.7 Hz, 2H), 7.17 (t, 8.4 Hz, 1H), 6.96 (m, 5H), 6.82 (d, 8.4 Hz, 1H), 4.62 (t, 6.2 Hz, 2H), 4.56 (s, 2H), 4.50 (s, 2H), 4.17 (s, 2H), 3.00 (t, 6.2 Hz, 2H), 2.36 (s, 3H). C₃₄H₃₁N₃O₅ = 550.23 (M + H⁺) by LC/MS (electrospray).

CC1=C(COP(=O)(OC(=O)NCCc2ccc(OCCc3ccc(OCCc4ccc(OCCc5ccc(OCCc6ccc(OCCc7ccc(OCCc8ccccc8)cc7)cc6)cc5)cc4)cc3)cc2)OC(=N1)C3=CC=CC=C3CC1=C(C(=N1C2=CC=CC=C2)COC3=CC=C(C=C3)CCCN4C(=O)OC(C)(C)C)OC5=CC=CC=C5

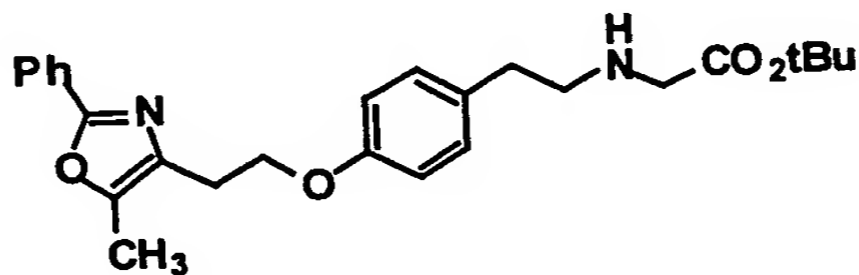
- 192 -

5

CCCC(=O)OCCN(CCCOc1ccc(OCC2=C(C)OC(=N2)C3=CC=CC=C3)cc1)S(=O)(=O)c1ccc([N+](=O)[O-])cc1Cc1c(Cc2ccc(OCCN(S(=O)(=O)c3ccc([N+](=O)[O-])cc3)cc2)oc1=N)c3ccccc3

To a solution of the crude 2,4-dinitrobenzene-sulfonamide in CH₃CN (3 mL) were added K₂CO₃ (excess) and tert-butyl bromoacetate (7.11 mmol). The reaction was stirred at RT overnight. HPLC analysis indicated the ratio of product to starting material was 2/1. More DMF (3 mL), K₂CO₃ and tert-butyl bromoacetate were added to the reaction mixture. The reaction was complete in 2 h. The reaction mixture was diluted with Et₂O, washed with 1N aq HCl, saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated in vacuo to provide the crude tert-butyl ester. This crude material was chromatographed (SiO₂; hexanes/EtOAc; stepwise gradient from 9:1 to 2:1) to give title compound (0.663 g, 42% overall).

15 C.

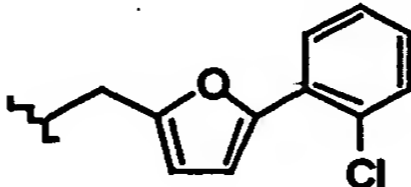
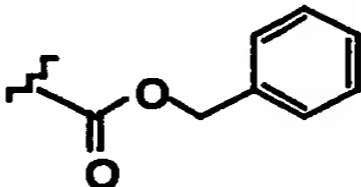
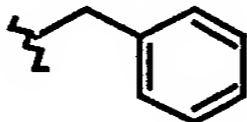


To a solution of Part B compound (0.663 g, 0.995 mmol) in THF (2.5 mL) were added Et₃N (0.208 mL, 1.49 mmol) and mercaptoacetic acid (0.090 mL, 1.29 mmol). The reaction was stirred at RT overnight. The reaction mixture was then diluted with Et₂O, washed with 1N aq HCl, saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed (SiO₂; hexanes/EtOAc; stepwise gradient from 9:1 to 2:1) to give title compound (0.265 g, 61%).

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)OCCN(CCC4=CC=C(C=C4)OC5=CC=CC=C5)CC(=O)O)C

Further analogs (as shown in the table below) were synthesized by the same reductive amination procedure as described in Example 459 Part D using Example 459 Part C compound and different aromatic aldehydes. In addition carbamate-acids such as Example 461 compound were also synthesized using the general method described previously for the synthesis of the Example 136 compound.

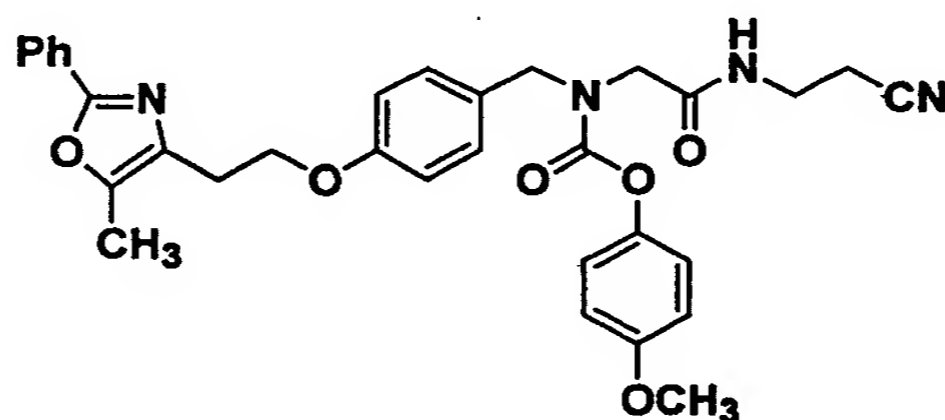
CC1=C(C(=O)O)C(=C(C1)C2=CC=CC=C2OCC3=CC=CC=C3)C(=O)N(C)C

Example No.	R ³	[M+H] ⁺
460		571.3
461		515.3
462		471.3

5

Cc1c(Cc2ccc(OCC3C(=N1)C(=O)N3C4=CC=CC=C4C5=CC=C(C=C5)OC)CC2)c(O)c2ccccc12

A.

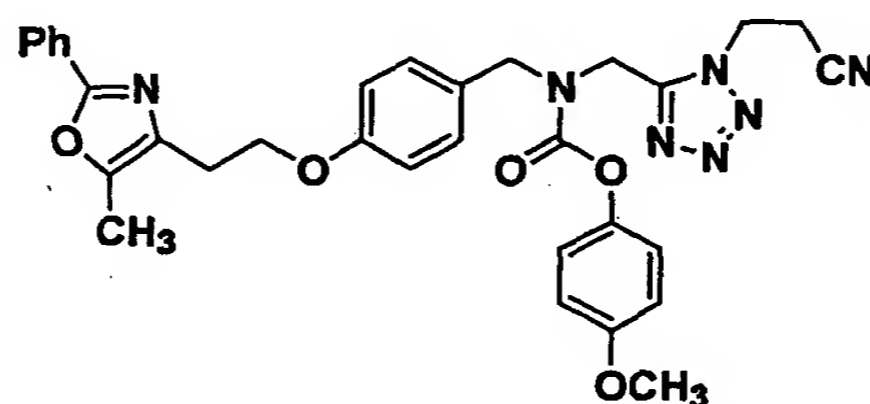


10

To a solution of the Example 230 acid (240 mg, 0.47 mmol) in DMF (2.0 mL) were added HOAT (68 mg, 0.49 mmol),
15 EDAC (94 mg, 0.49 mmol) and 2-cyanoethylamine (34 mg, 0.49 mmol). The solution was stirred at RT for 18 h;

analysis of the reaction by LC-MS showed that starting material was still present. Additional 2-cyanoethylamine (34 mg, 0.49 mmol) was added and the reaction mixture was stirred at RT for 48 h. Volatiles were removed in vacuo and the residue was dissolved in CH₂Cl₂ (40 mL) and washed successively with water (2 x 30 mL) and brine (30 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The resulting white residue was dissolved in a minimum amount of CH₂Cl₂ (3 mL) and precipitation by the cautious addition of EtOAc furnished the amide product title compound (184 mg; 70%) as a white solid.

B.

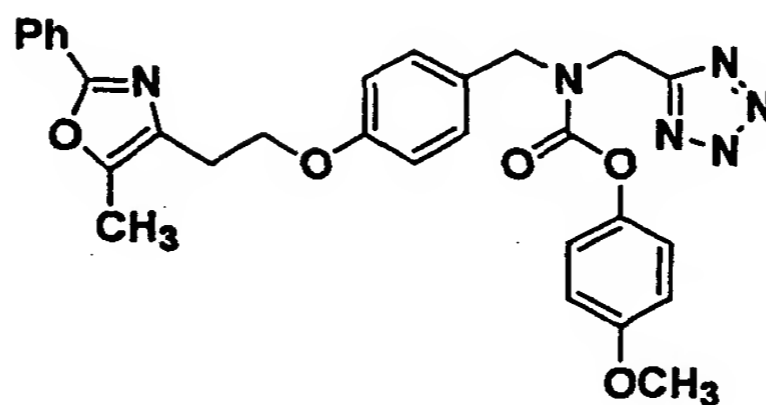


15

To a 0°C solution of Part A compound (180 mg; 0.32 mmol) in CH₂Cl₂ (1.5 mL) were successively added Ph₃P (83 mg; 0.32 mmol), DEAD (100 μL, 0.64 mmol) and TMSN₃ (85 uL, 0.64 mmol). The reaction mixture was stirred at RT for 24 h. LC-MS analysis showed that a significant amount of starting material still remained. The reaction mixture was then concentrated in vacuo to 2/3 of the original volume and additional Ph₃P, DEAD and TMSN₃ (1 equivalent of each reagent) were added. The reaction mixture was stirred at RT for another 24h and then diluted with EtOAc (40 mL). The solution was treated with 5% aqueous CAN solution (10 mL) and stirred for 15 min. The reaction solution was washed with water (30 mL) and brine (30 mL), dried (MgSO₄) and concentrated in vacuo. The residue was

chromatographed (SiO_2 ; ether: CH_2Cl_2 3:7) to furnish the title compound (100 mg; 53%) as a white solid.

C.

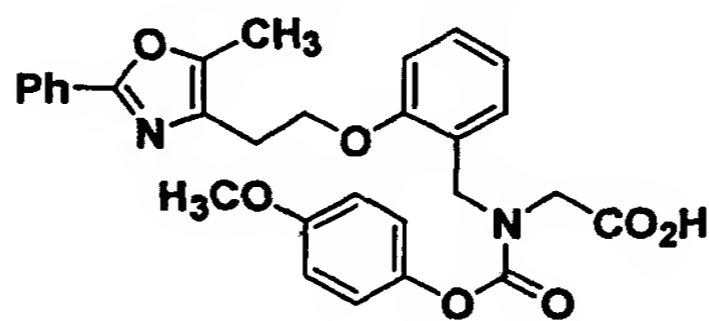


5

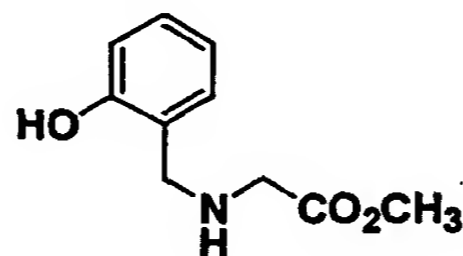
To a solution of Part B compound (100 mg, 0.17 mmol) in THF/1,4-dioxane (6:1, 1.4 mL) was added aqueous NaOH solution (0.6 mL of a 1.0 M solution, 3.5 equiv). The mixture was stirred at RT for 14 h and then acidified to ~pH 2 with 1.0 M aqueous H_3PO_4 solution. EtOAc (30 mL) was added, and the organic phase was washed with water (15 mL) and brine (15 mL), dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; 4% MeOH/ CH_2Cl_2) to give the title tetrazole (35 mg; 38%) as a white foam. LC/MS (electrospray) gave the correct molecular ion: $[\text{M} + \text{H}]^+ = 541.3$

20

Example 464



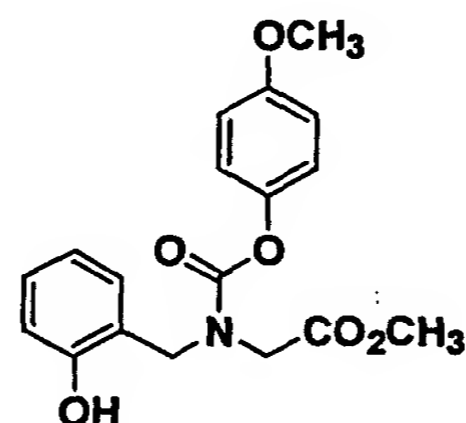
A.



25

A mixture of 2-hydroxybenzaldehyde (500 mg, 4.09 mmol), glycine methyl ester hydrochloride (544 mg, 4.09 mmol) and Et₃N (495 mg, 4.9 mmol) in dry MeOH (5 mL) was stirred at RT for 3 h. NaBH₄ (155 mg, 4.09 mmol) was then added in three portions. The reaction was stirred at RT for another 30 min. Saturated aqueous Na₂CO₃ (1 mL) was added to destroy the remaining NaBH₄ and then aqueous HCl (10 mL of a 1N solution) was added. The aqueous phase was washed with EtOAc (3 x 20 mL), then carefully basified with 1N aq NaOH to pH = 7-8. The aqueous phase was then extracted with EtOAc (3 x 20 mL). The orange-red solution was concentrated *in vacuo* to give title compound as a yellow viscous oil.

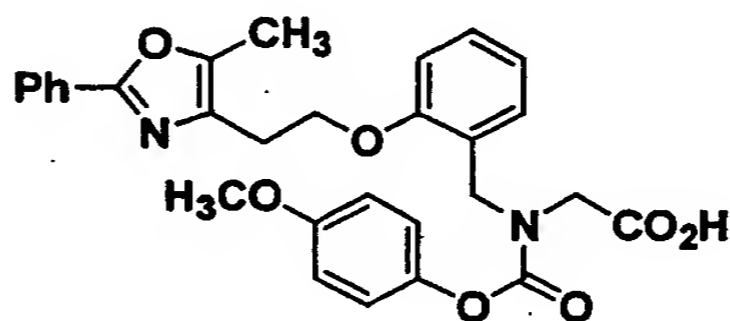
15 B.



Part A compound (38 mg, 0.195 mmol), 4-methoxyphenyl chloroformate and pyridine (39 mg, 5 mmol) was dissolved in 0.1 mL CH₂Cl₂, for 5 min. The reaction mixture was then washed with aqueous HCl (2 x 2 mL of a 1N solution). The organic phase was washed with brine, dried (Na₂SO₄), concentrated *in vacuo* and chromatographed (SiO₂; hex:EtOAc = 7 :3) to give title compound (40 mg; 59%) as a pale yellow oil.

COC(=O)N(Cc1ccccc1OCCc2c(C)c(Oc3ccccc3)nc2c4ccccc4)c5ccc(OC)cc5

D.

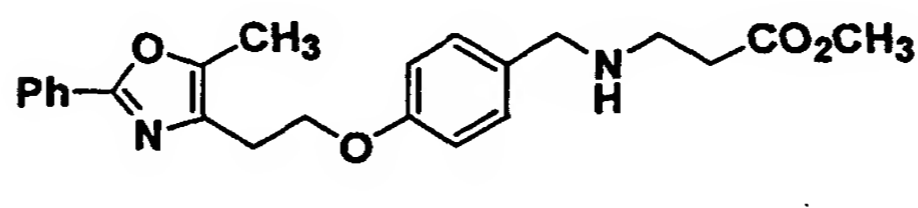


Part C compound was dissolved in MeOH (3 mL) and H₂O (0.3 mL). To this solution was added LiOH (3 mg) and the reaction was stirred at RT for 3 h. Volatiles were removed *in vacuo* and the solution was acidified with 1N aqueous HCl to pH = ~3-4. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give title compound as a white solid (18 mg; 64%). LC/MS (electrospray) gave the correct molecular ion [(M+H)⁺ = 516].

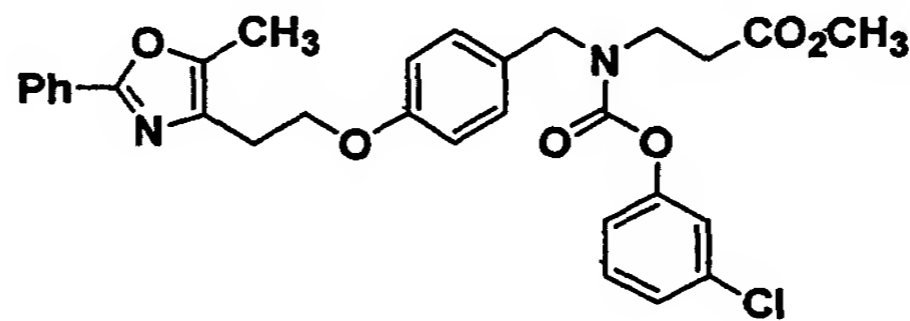
5

CC1=C(CCOc2ccc(cc2)COC(=O)NCC(=O)O)N=C(c3ccccc3)O1

A.

CC1=C(CCOc2ccc(C=O)cc2)N(=C1)c3ccccc3

B.



- 201 -

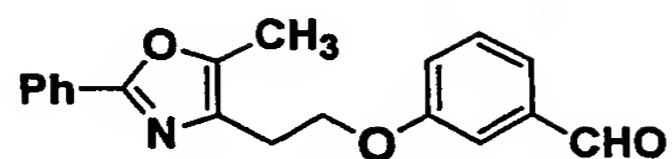
5

CC1=C(CCOc2ccc(cc2)COC(=O)NCC(=O)O)N=C(c3ccccc3)O1

A solution of Part B compound and LiOH.H₂O (5 mg) in THF:H₂O (4:1) was stirred at RT for 1 h. The reaction solution was acidified to pH 3 with aqueous HCl, then extracted with EtOAc. The combined organic extracts were concentrated in vacuo to give title compound (5 mg; 18%) as a white solid. $[M + H]^+ = 535.2; 537.2$

CC1=C(COCC2=CC=C(C=C2)OC(=O)NCC(=O)O)N=C(C1)c3ccccc3

Title compound was synthesized using the same sequence as in Example 465 with the exception that the aldehyde



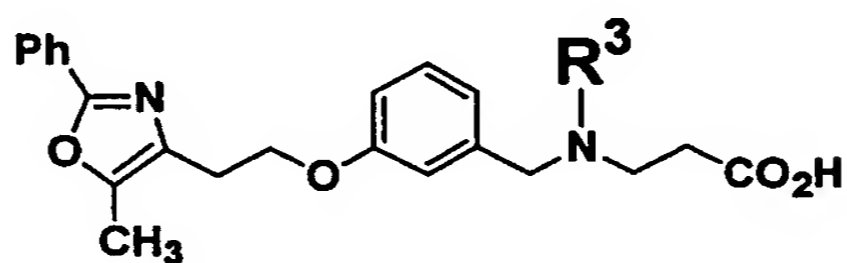
was used. $[M + H]^+ = 535.2; 537.2$

5

Following procedures as described above, Examples 467 to 472 compounds were prepared.

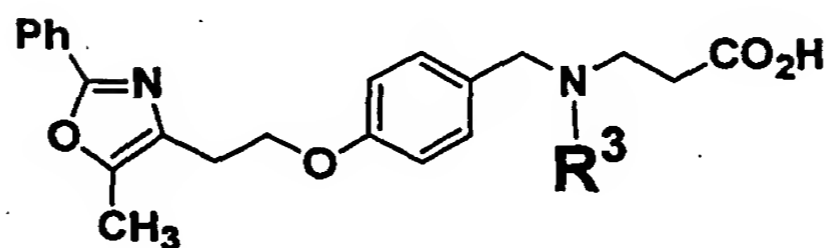
Examples 467 to 469

10



Example No.	R ³	[M+H] ⁺
467		501.3
468		563.3
469		515.3

Examples 470 to 472

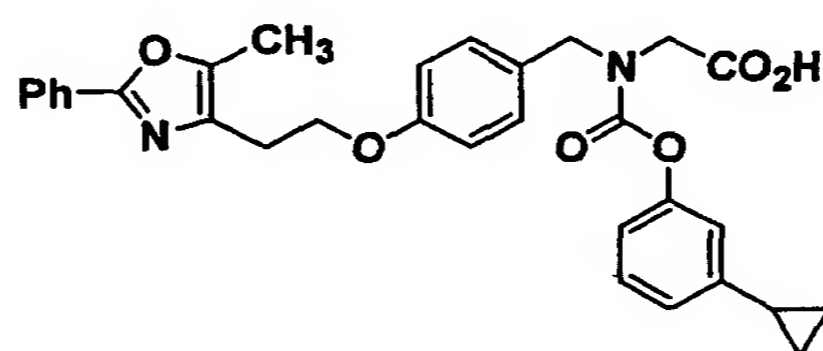


5

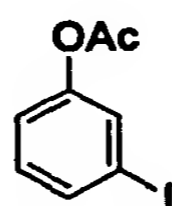
Example No.	R ³	[M+H] ⁺
470		501.3
471		563.3
472		515.3

Example 473

10



A.

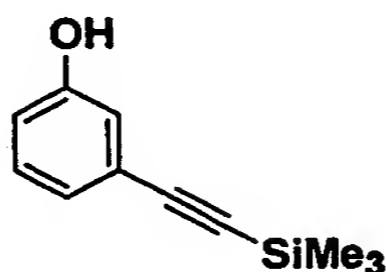


15

A mixture of 3-iodophenol (2.0 g; 9.1 mmol), acetic anhydride (4.6 g; 45.5 mmol) and pyridine (3.6 g; 45.5 mmol) was stirred in CH_2Cl_2 (20 mL) for 3 h. The resulting mixture was washed with saturated aqueous NH_4Cl

(3 x 100 mL), dried (MgSO_4) and concentrated in vacuo to give Part A compound (2.30 g; 97%) as a yellow oil.

B.

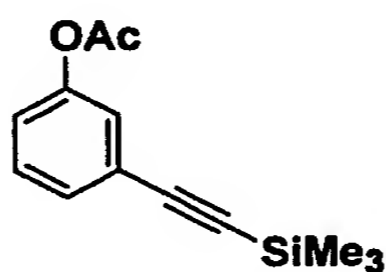


5

A mixture of Part A compound (1.00 g; 4.0 mmol), trimethylsilylacetylene (780 mg; 8 mmol), CuI (15 mg; 0.08 mmol) and $(\text{Ph}_3\text{P})_2\text{Pd}_2\text{Cl}_2$ (28 mg; 0.04 mmol) in diethylamine (10 mL) was stirred at RT for 3 h. Volatiles were removed in vacuo and the residue was chromatographed (SiO_2 ; hexane:EtOAc 4:1) to give crude Part B compound, which was used in the next step without further purification.

15

C.

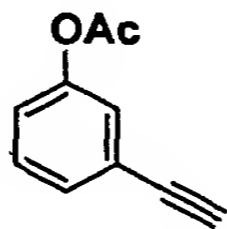


20

To a solution of crude Part B compound in CH_2Cl_2 (2 mL) were added pyridine (3 mL; 37 mmol) and acetic anhydride (4 mL; 42 mmol). The reaction was stirred at RT for 2 h, then was partitioned between saturated aqueous NH_4Cl (30 mL) and CH_2Cl_2 . The organic phase was washed with additional saturated aqueous NH_4Cl (30 mL) and H_2O (100 mL), dried (Na_2SO_4) and concentrated in vacuo to give Part C compound, which was used in the next step without further purification.

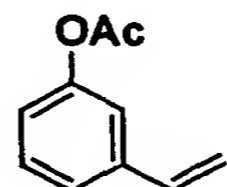
30

D.



5 A solution of crude Part C compound and Bu_4NF (1.1 g; 12 mmol) in THF (10 mL) was stirred at RT for 1.7 h, after which all starting material had been consumed. The reaction solution was washed with H_2O , Celite[®] was added, and volatiles were removed in vacuo. The solids were
10 chromatographed (SiO_2 ; hexane:EtOAc 9:1) to give Part D compound (400 mg; 63% over 3 steps).

E.

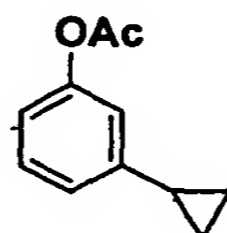


15

A mixture of Part D compound (400 mg; 2.5 mmol) and Pd/ CaCO_3 /Pb catalyst (40 mg; Aldrich) in MeOH (20 mL) was stirred under an atmosphere of H_2 for 30 min. The mixture
20 was filtered through Celite[®] and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO_2 ; hexane:EtOAc 95:5) to give Part E compound (310 mg; 77%) as a colorless oil.

25

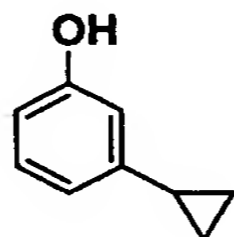
F.



To a 0°C solution of Part E compound (310 mg; 1.9
30 mmol) in DCE (10 mL) were successively added dropwise neat diethylzinc (491 μL ; 4.8 mmol; Aldrich) and ICH_2Cl (700 μL ; 9.6 mmol). The reaction mixture was allowed to

warm to RT and then stirred at RT for 3 h, after which it was partitioned between saturated aqueous NH_4Cl and EtOAc (50 mL each). The organic phase was washed with saturated aqueous NH_4Cl and H_2O (50 mL each) and concentrated in vacuo. The residue was chromatographed (SiO₂; hexane:EtOAc 9:1) to furnish Part F compound (230 mg; 69%) as a colorless oil.

G.

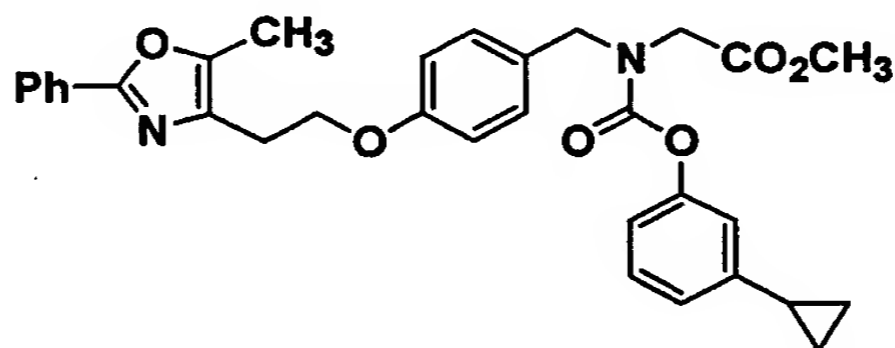


10

A mixture of Part F compound (100 mg; 0.57 mmol) and K_2CO_3 (157 mg; 1.1 mmol) in MeOH (5 mL) was stirred at RT overnight (no reaction). Aqueous LiOH (1.1 mL of a 1 M solution; 1.1 mmol) was added and the solution was stirred at RT overnight. Volatiles were removed in vacuo and the residue was partitioned between aqueous 1 M HCl and EtOAc. The organic phase was concentrated in vacuo and the residue was chromatographed (SiO₂; hexane:EtOAc 4:1) to furnish Part G compound (70 mg; 92%) as a yellow oil.

20

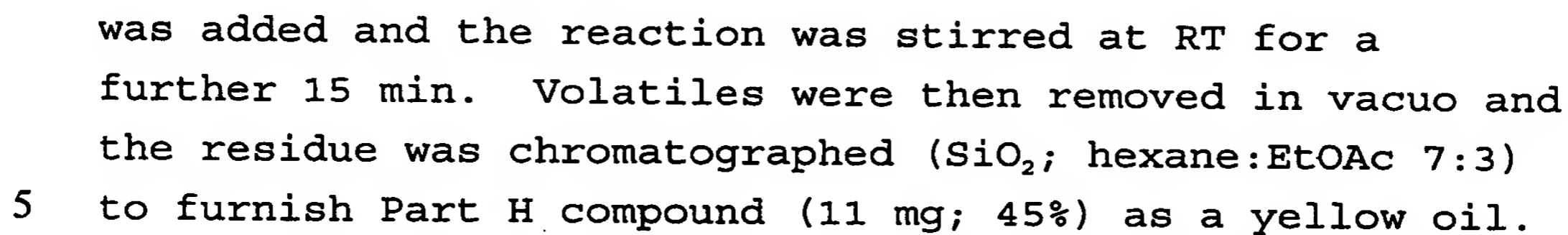
H.



25

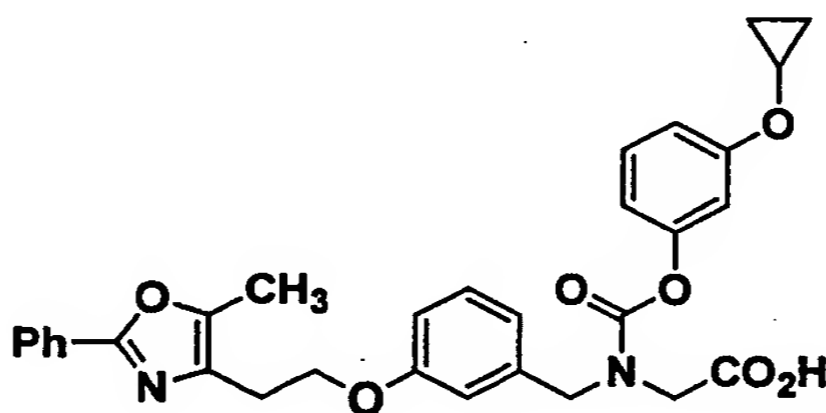
To a solution of Part G compound (6 mg; 0.045 mmol) in DMF (0.2 mL) was added potassium t-butoxide (5 mg; 0.05 mmol). The reaction was stirred for 2 min at RT, after which the carbamoyl chloride (20 mg; 0.045 mmol)

30

CC1=C(CCOc2ccc(cc2)COC(=O)NCC(=O)O)N=C(c3ccccc3)O1Cc4ccc(cc4)C5CC5

A solution of Part H compound and LiOH.H₂O in MeOH/H₂O (10 mL of a 9:1 mixture) was stirred at RT overnight. The solution was then acidified to pH ~3 with aqueous HCl and extracted with EtOAc. The combined
15 organic extracts were concentrated in vacuo and purified by preparative HPLC to give title compound (10.1 mg; 95%) as an off-white lyophilate. [M + H]⁺ = 527.3

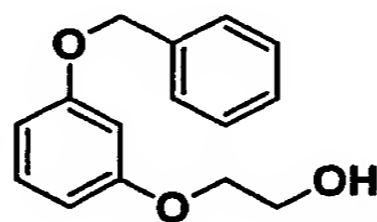
20

CCOC(=O)COc1ccccc1Oc2ccccc2

- 208 -

A mixture of 3-benzyloxybenzaldehyde (2.00 g; 1.0 mmol), ethyl bromoacetate (1.67 g; 1.0 mmol) and Cs_2CO_3 (3.25 g; 1.0 mmol) in DMF (20 mL) was stirred at RT for 8 h. The reaction mixture was partitioned between H_2O (300 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; 85:15 hex:EtOAc) to obtain Part A compound (3.48 g; >100%) as a colorless oil.

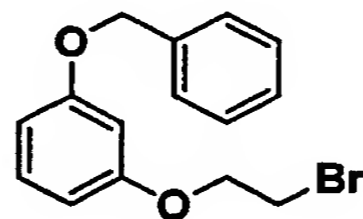
B.



15

To a solution of Part A compound (3.4 g; 11.9 mmol) in dry THF (50 mL) under Ar was added LiAlH_4 (36 mL of a 0.5 M solution in THF; 17.8 mmol) dropwise. The reaction was stirred at RT for 1 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (1 mL). Volatiles were removed in vacuo and the residue was partitioned between EtOAc (100 mL) and 1 M aqueous HCl. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give Part B compound (2.4 g; 98%) as a white solid.

C.

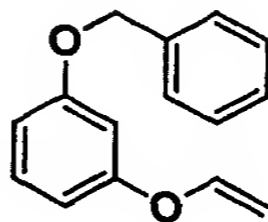


30

To a solution of Part B compound (2.4 g; 9.8 mmol) and Ph_3P (3.1 g; 14.7 mmol) in CH_2Cl_2 was added CBr_4 (4.80 g; 14.7 mmol). The reaction was stirred at RT overnight, then concentrated in vacuo. The residue was

chromatographed (SiO_2 ; 95:5 hex:EtOAc) to give Part C compound (2.8 g; 93%) as a white solid.

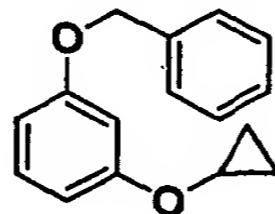
D.



5
10 A mixture of Part C compound (310 mg; 1.0 mmol) and potassium tert-butoxide (113 mg; 2.0 mmol) in toluene (20 mL) was heated at 105°C for 20 min. Additional K_{OT}Bu (56 mg; 1.0 mmol) was added and the reaction heated at 105°C for another 10 min. The mixture was cooled to RT and partitioned between H₂O (100 mL) and EtOAc (100 mL). The organic phase was washed with H₂O (2 x 100 mL), dried
15 (Na_2SO_4) and concentrated in vacuo. The reaction was repeated with additional Part C compound (500 mg; 1.63 mmol) and K_{OT}Bu (182 mg; 16 mmol). The combined crude reaction products were chromatographed (SiO_2 ; hexane) to give Part D compound (590 mg; 89%) as a colorless oil.

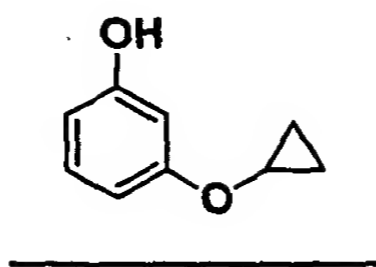
20

E.



25 To a 0°C solution of Part D compound (1.4 g; 62 mmol) in DCE (100 mL) was added neat diethylzinc (1.6 mL; 16 mmol) dropwise, followed by ICH_2Cl (5.46 g; 31 mmol). The reaction mixture was allowed to warm to RT and stirred at RT overnight, then washed with 1M aqueous HCl.
30 The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was chromatographed twice (SiO_2 ; hexane) to give Part E compound (510 mg; 30%) in addition to recovered starting material Part D compound (250 mg; 18%).

F.

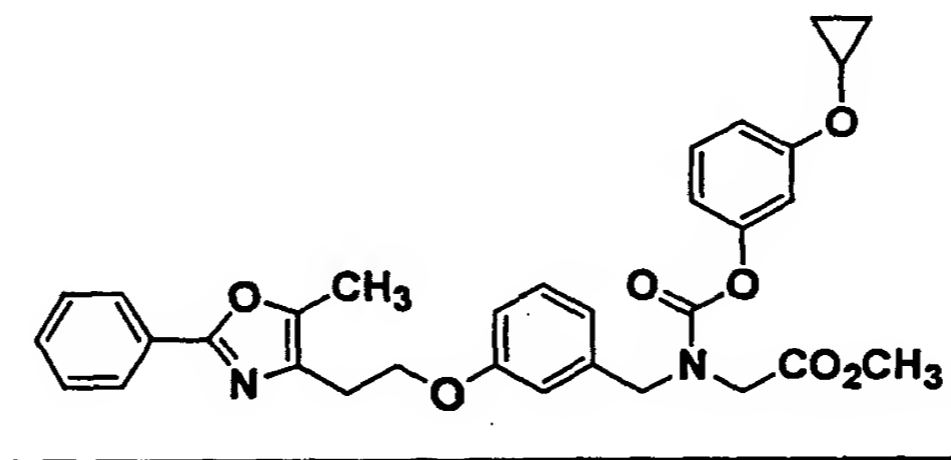


5

To a -78°C solution of Part E compound (510 mg; 2.2 mmol) in liquid NH_3 (30 mL) was added Na (500 mg; 22 mmol). The dark blue solution was stirred at -78°C for 4 h, then was allowed to warm to RT overnight. The remaining solid residue was partitioned between 1 M aqueous HCl and EtOAc (50 mL each). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was chromatographed (SiO_2 ; 9:1 hexane:EtOAc) to give Part F compound (240 mg; 75%) as a yellow oil.

15

G.



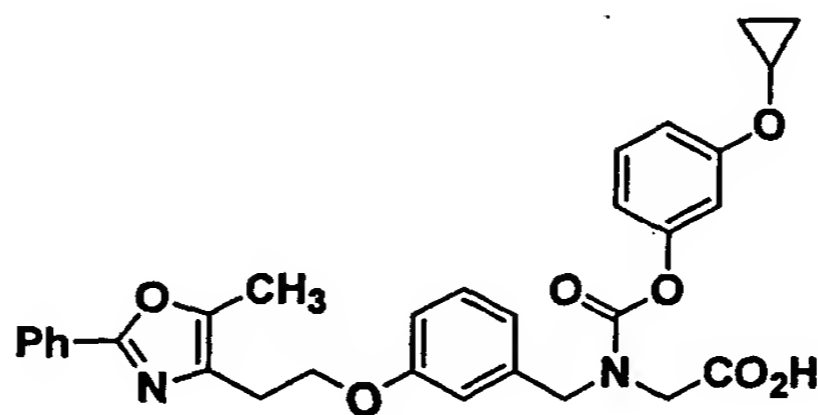
To a solution of Part F compound (150 mg; 1.0 mmol) in DMF (10 mL) were successively added K₂CO₃ (112 mg; 1.0 mmol) and a solution of the following carbamoyl chloride (44 mg; 1.0 mmol) in DMF (0.5 mL).

25 (prepared as described in Examples 5 and 139). The reaction was stirred at RT for 15 min, after which analytical HPLC indicated that all starting material had been consumed. The mixture was partitioned between H_2O and EtOAc (100 mL each). The organic phase was washed with H_2O (2 x 100 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was

30

chromatographed (SiO_2 ; 9:1 hexane:EtOAc) to give impure Part G compound as a yellow oil.

H.

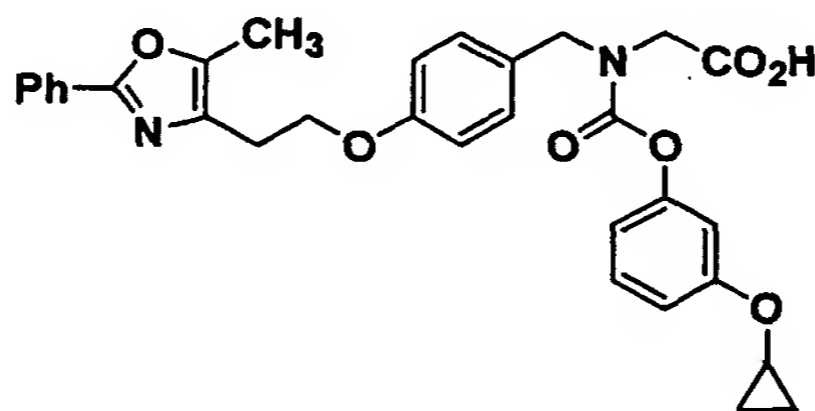


5

A solution of Part G compound (556 mg; 1.0 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (116 mg; 2.8 mmol) in 10:1 MeOH: H_2O (10 mL) was stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was acidified to pH 2 with aqueous 1 M HCl, then extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by preparative HPLC (YMC S5 ODS 50 x 250 mm column; flow rate = 25 mL/min; continuous 20 min gradient from 70:30 B:A to 100% B, where A = 90:10:0.1 H_2O :MeOH:TFA and B = 90:10:0.1 MeOH: H_2O :TFA) to give (120 mg; 30% over 2 steps) as a colorless oil. $[\text{M} + \text{H}]^+ = 543.2$

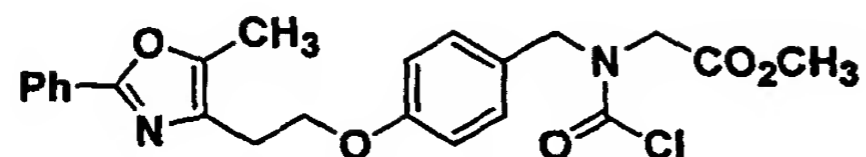
20

Example 475



25

Title compound was synthesized from Example 474 Part F compound (150 mg; 1.0 mmol) and the carbamoyl chloride (440 mg; 1.0 mmol)

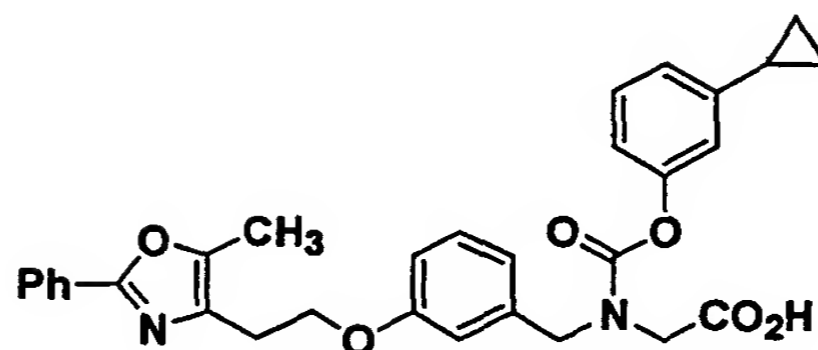


(prepared as described in Examples 6 and 139) followed by LiOH/H₂O hydrolysis in the same manner as in Example 474.

- 5 The title compound was isolated and purified as a colorless oil (340 mg; 92% over 2 steps). [M + H]⁺ = 543.3



- 214 -

Example 492

5

Example 492 was synthesized according to the procedures described hereinbefore.

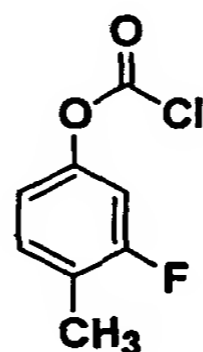
¹H NMR (CDCl₃; 400 MHz): δ 0.68 (t, J = 4.4 Hz; 2H), 0.94 (t, J = 4.4 Hz; 2H), 1.87 (m, 1H), 2.42 (s, 3H), 3.06 (s, 2H), 4.02 (t, J = 5.2 Hz, 2H), 4.22 (t, J = 5.2 Hz, 2H), 4.60 (2 peaks, 2H), 6.84-6.89 (m, 4H), 7.15-7.26 (m, 4H), 7.40-7.47 (m, 3H), 7.98-8.00 (m, 2H).

15

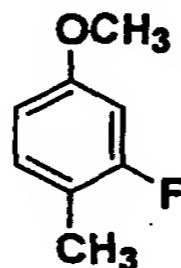
The required (commercially unavailable) phenols and chloroformates for the synthesis of the above carbamate-acid analogs were prepared as follows:

3-Fluoro-4-methyl-phenyl chloroformate

20



A.



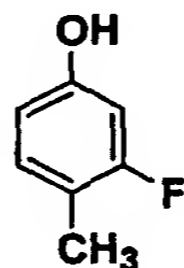
25

A mixture of 5-methoxy-2-methyl aniline (5.0 g; 36 mmol), HCl (7.6 mL of a 12 M solution; 91 mmol) and H₂O (11 mL) was heated at 60°C for 15 min until complete dissolution had occurred. The reaction was cooled to 0°C

and an aqueous solution of NaNO_2 (2.5 g; 36 mmol) was added dropwise (internal temperature $\leq 7^\circ\text{C}$). The reaction was stirred at 0°C for 30 min and a 0°C solution of HBF_4 (5.3 mL of a 48% solution; 40 mmol) was added cautiously.

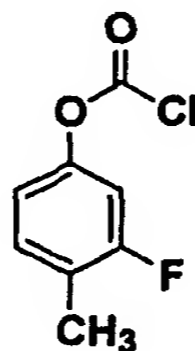
5 The reaction was stirred at 0°C for 20 min, and the resultant brown solid was filtered, washed with ice water (3 x 10 mL) and H_2O (2 x 10 mL). The solid was dried under high vacuum for 20 h, then heated (heat gun) until evolution of BF_3 (white fumes) had ceased. The resulting
10 brown oil was partitioned between EtOAc and H_2O . The organic phase was dried (Na_2SO_4), concentrated in vacuo and distilled by Kugelrohr to give 3-fluoro-4-methyl anisole (1.6 g; 31%) as a colorless oil.

15 B.



To a -70°C solution of 3-fluoro-4-methyl anisole (1.62 g; 11.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise
20 BBr_3 (10 mL; 12 mmol). The reaction mixture was stirred at -70°C for 10 min, then allowed to warm to 0°C and stirred at 0°C for 2 h. The reaction was allowed to warm to RT and concentrated in vacuo and the residue was
25 partitioned between H_2O and EtOAc. The organic phase was washed with H_2O , dried (Na_2SO_4) and concentrated in vacuo to give 3-fluoro-4-methyl phenol (1.1 g; 75%) as an oil.

C.

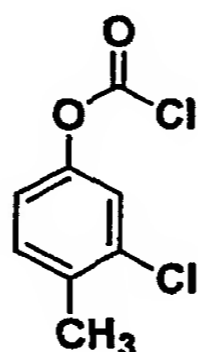


30

A solution of 3-fluoro-4-methyl phenol (1.1 g; 8.7 mmol), phosgene (5.9 mL of a 1.93 M solution in toluene;

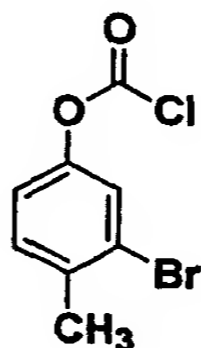
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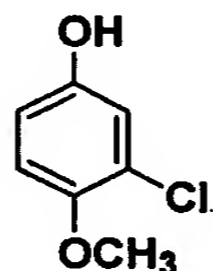
(1.72 g; 34%) as an oil. This phenol was converted to 3-bromo-4-methyl phenyl chloroformate (1.9 g; 82%) using the same procedure (phosgene/ dimethylaniline/heat) as for 3-fluoro-4-methyl phenyl chloroformate above.

5

2-Methoxyphenyl chloroformate (1.5 g) and 3-methoxyphenyl chloroformate (1.5 g) were both synthesized in the same way as for 3-fluoro-4-methyl phenyl chloroformate (phosgene/dimethylaniline/heat) from 2-methoxyphenol (2 g) and 3-methoxyphenol (2 g) respectively.

10

3-chloro-4-methoxy phenol



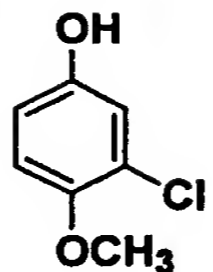
15

To a 0°C solution of 3-chloro-4-methoxy aniline (1.0 g; 6.4 mmol) in 1:1 H₂O:conc. H₂SO₄ (100 mL) was added very slowly a solution of NaNO₂ (0.5 g; 7.6 mmol) in H₂O (10 mL). Thick yellow fumes were emitted, and the black solution was then heated to reflux for 30 min. The mixture was extracted with EtOAc (4 x 50 mL) and the combined extracts were concentrated in vacuo. The residue was chromatographed (SiO₂; 4:1 hex:EtOAc) to obtain 3-chloro-4-methoxy phenol (300 mg; 30%) as a yellow oil.

20

25

3-Fluoro-4-methoxy-phenol

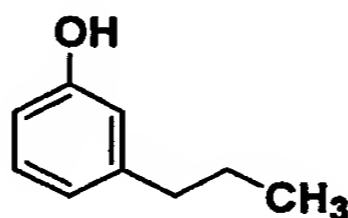


30

A solution of 3'-fluoro-4'-methoxyacetophenone (10 g; 59 mmol) and m-chloroperbenzoic acid (50% purity; 30

15 3-bromo-4-methoxy phenol (4.39 g; 47% for 2 steps)
was synthesized using the exact analogous sequence
starting from 3-bromo-4-methoxy benzaldehyde.

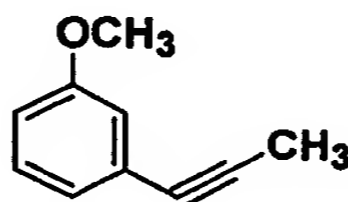
20

COc1ccc(C#C)cc1

30 Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and brine. The organic phase was washed with brine (2 x 10 mL) and then filtered through a pad of SiO₂. Volatiles were removed in vacuo to give the crude product (3-trimethylsilylethynyl anisole)

as a light yellow oil. A solution of this crude product and tetrabutylammonium fluoride (6.6 g; 26 mmol) in THF (10 mL) was stirred at RT for 15 min. Volatiles were removed in vacuo and the residue was chromatographed (SiO₂; 9:1 hex:EtOAc) to furnish Part A compound (1.0 g; 89%) as a yellow oil.

B.

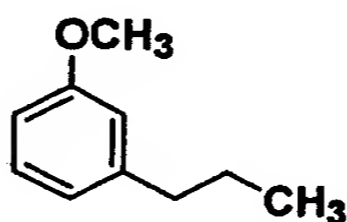


10

To a 0°C solution of Part A compound (1.0 g; 7.6 mmol) in anhydrous THF (5 mL) was added dropwise n-BuLi (4.5 mL of a 2.0 M solution in hexane; 9.1 mmol). The resulting yellow solution was stirred at 0°C for 30 min. Methyl iodide (1.6 g; 11.4 mmol) was then added and the reaction was allowed to warm to RT and stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between aqueous 1N HCl and EtOAc. The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo to give Part B compound (1.0 g; 92%) as a yellow oil.

15

C.

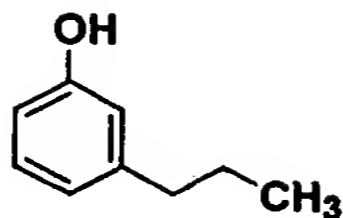


25

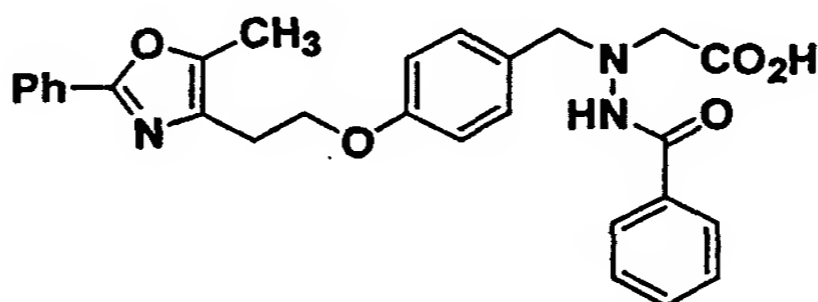
A solution of Part B compound (1.0 g) in MeOH (5 mL) was stirred over 10% Pd/C (10 mg) under an atmosphere of H₂ overnight. The catalyst was removed by filtration through a pad of Celite® and the filtrate was concentrated in vacuo to give Part C compound (1.0 g; 100%) as a yellow oil.

30

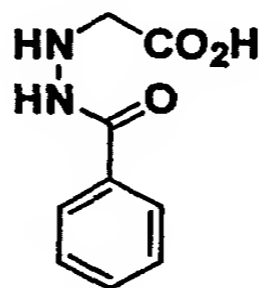
D.



To a -78°C solution of Part C compound (1.0 g; 6.6 mmol) in CH_2Cl_2 (10 mL) was added BBr_3 (4.8 mL of a 1 M solution in CH_2Cl_2). The reaction was allowed to warm to RT and was stirred at RT for 3 h, after which it was cautiously partitioned between aqueous 1 M HCl and CH_2Cl_2 . The organic phase was washed with aqueous NH_4Cl , dried (MgSO_4) and concentrated in vacuo to give 3-propyl phenol (900 mg; 100%) as a yellow oil.

Example 495

A.

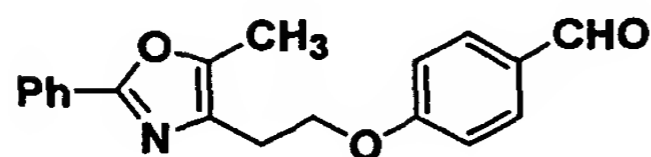


20

A mixture of benzoic acid (1.22 g; 10 mmol), methanesulfonyl chloride (1.15 g; 10 mmol), K_2CO_3 (5.52 g; 40 mmol) and benzyltriethylammonium chloride (0.23 g; 1 mmol) in toluene was stirred at 80°C for 2 h. Ethyl hydrazine acetate hydrochloride (1.55 g; 10 mmol) was then added and the reaction was stirred for a further 30 min, then cooled to RT. Solids were filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO_2 ; stepwise gradient from 3:1 to 1:1 hexane:EtOAc) to give Part A compound (350 mg; 16%) as a white solid.

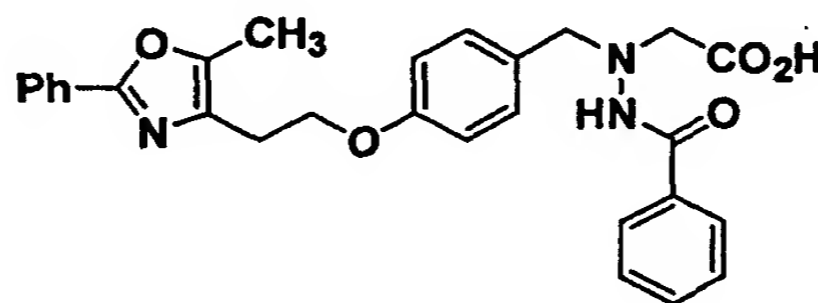
CC1=C(CCOc2ccc(cc2)CN(CCN(C(=O)c3ccccc3)C(=O)OCC)Cc4ccccc4)N=C(C1)c5ccccc5

To a 0°C solution of Part A compound (49 mg; 0.22 mmol) and the aldehyde (50 mg; 0.10 mmol)



20

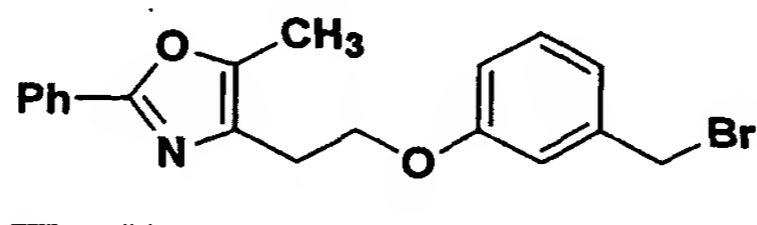
C.



A solution of crude Part B compound in THF (1 mL) and aqueous LiOH (0.3 mL of a 1 M solution; 0.3 mmol) was stirred at RT for 3 h, then acidified to pH ~3 with aqueous 1 M HCl. The aqueous phase was extracted with EtOAc (2x); the combined organic extracts were concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; 22 min continuous gradient from 70:30 B:A to

5

10



15

CC1=C(CCCOC2=CC=CC=C2C=CC=C2C=O)N(=C1)C3=CC=CC=C3

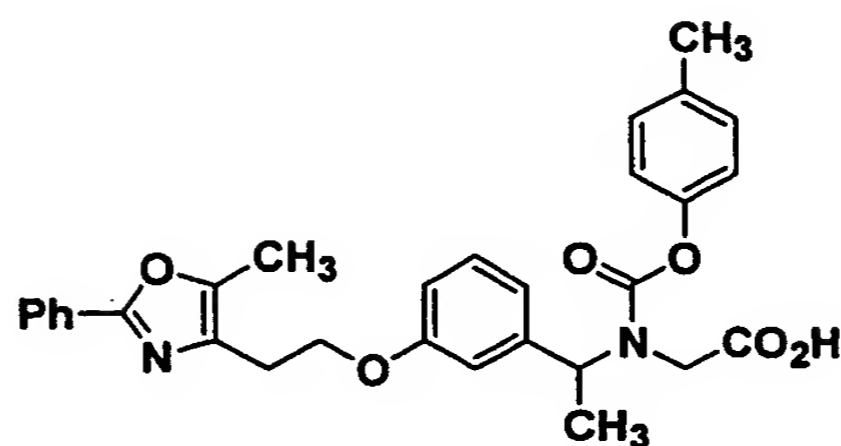
20

in MeOH (2 mL) was added portionwise NaBH_4 (24 mg; 0.65 mmol), after which the reaction was allowed warm to RT and stirred at RT for 1 h. Volatiles were removed in vacuo and the residue was partitioned between H_2O and EtOAc. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the intermediate alcohol as an oil. A solution of the alcohol in CH_2Cl_2 (2 mL) and PBr_3 (1 mL of a 1M solution in CH_2Cl_2) was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between aqueous saturated NaHCO_3 and EtOAc. The organic phase was washed with H_2O , dried (Na_2SO_4) and concentrated in vacuo to give Part A compound (150 mg; 62%) as an oil.

30

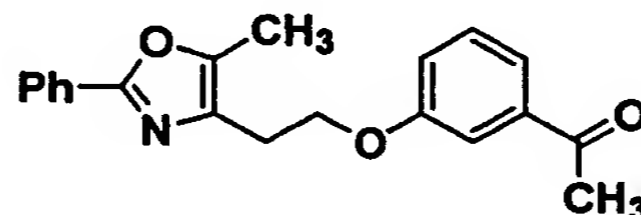
CC1=C(CCOc2ccc(cc2)CN(CCN(C1)c3ccccc3)C(=O)O)C(=Nc4ccccc4)O

5 Example 500 Part A compound (25 mg; 0.11 mmol) and K_2CO_3
(100 mg; 0.71 mmol) in DMF (1 mL) was stirred at RT for 3
days. The reaction mixture was partitioned between EtOAc
and H_2O . The organic phase was washed with H_2O (2x) and
concentrated in vacuo. The residual oil was dissolved in
10 THF (1 mL) and aqueous LiOH (0.3 mL of a 1 M solution)
was added. The reaction was stirred at RT for 3 h, then
acidified to pH ~3 with aqueous 1 M HCl. The aqueous
phase was extracted with EtOAc (2x); the combined organic
extracts were concentrated in vacuo. The residue was
15 purified by preparative HPLC (YMC S5 ODS 30 x 250 mm
column; flow rate = 25 mL/min; 20 min continuous gradient
from 70:30 B:A to 100% B, where solvent A = 90:10:0.1
 H_2O :MeOH:TFA and solvent B = 90:10:0.1 MeOH: H_2O :TFA) to
give title compound (15 mg; 27% yield over 2 steps) as a
20 white solid. $[M + H]^+ = 486.4$

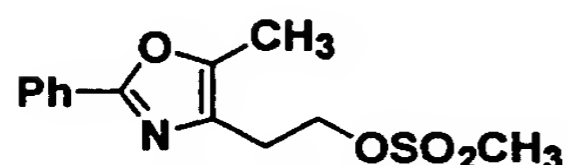
Example 497

5

A.

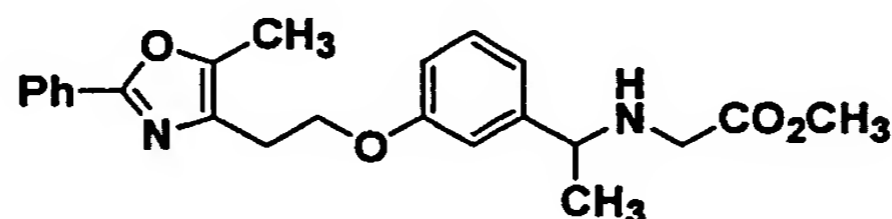


10 A mixture of 3-hydroxyacetophenone (650 mg; 4.78 mmol), K_2CO_3 (660 mg; 4.78 mmol) and the 2-phenyl-5-methyl-4-oxazole-ethanol mesylate (1.12 g; 3.98 mmol)



15 in MeCN (40 mL) was refluxed overnight. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc (100 mL) and 1.0 M aqueous NaOH (80 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; hexane:EtOAc 3:1) to give Part A
20 compound (850 g; 67%) as a yellow solid.

B.



25

To a solution of Part A compound (850 mg, 2.65 mmol) in DCE (15 mL) were successively added glycine methyl ester hydrochloride (333 mg, 2.65 mmol), Et_3N (554 μ L, 4.0 mmol), $NaBH(OAc)_3$ (786 mg; 3.7 mmol) and acetic

15

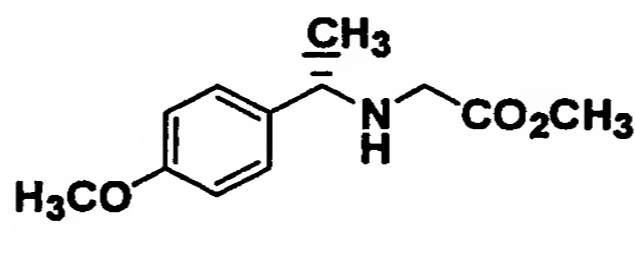
CCOC(=O)CN(C)c1ccc(OCCc2c(C)c(O)c(Cn3ccccc3)c2)cc1Oc4ccc(C)cc4

25

CC1=C(C=C(C=C1)OCCc2c(C)c(Oc3ccccc3)n2)C(C)N(C(=O)OC(=O)O)C(=O)Oc4ccc(C)cc4

5 Volatiles were removed in vacuo and the residue was
acidified to pH 2 with aqueous 1 M HCl, then extracted
with EtOAc (3 x 40 mL). The combined organic extracts
were dried (Na₂SO₄) and concentrated in vacuo. The crude
product was purified by preparative HPLC (YMC S5 ODS 50 x
10 250 mm column; flow rate = 25 mL/min; continuous 20 min
gradient from 70:30 B:A to 100% B, where A = 90:10:0.1
H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give title
compound (28 mg; 72% over 2 steps) as a white solid.
[M + H]⁺ = 515.3

Example 498.



- 228 -

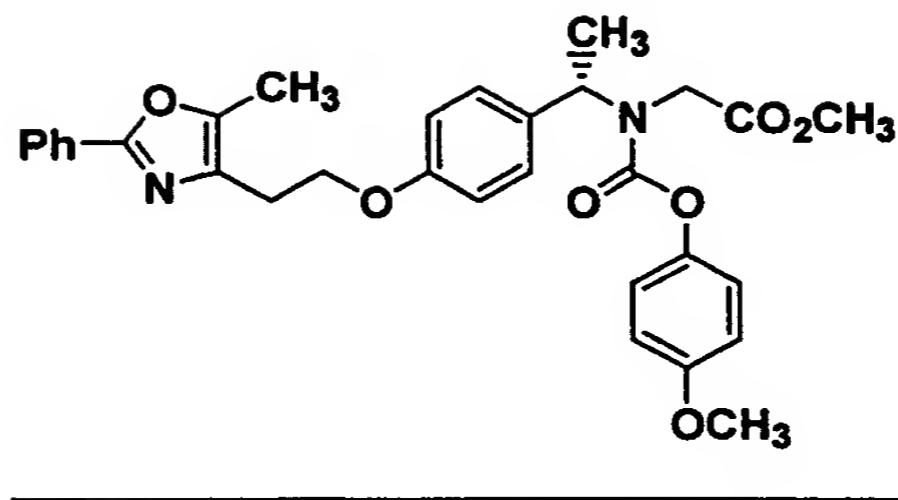
CCOC(=O)CN(C)c1ccc(O)cc1

15

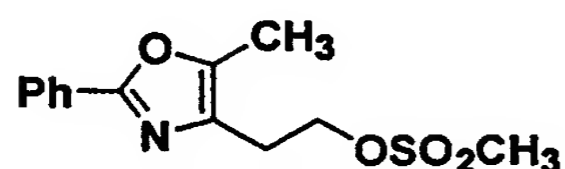
COc1ccc(Oc2c(=O)nc(C)c3ccc(O)cc3)cc1

25

D.

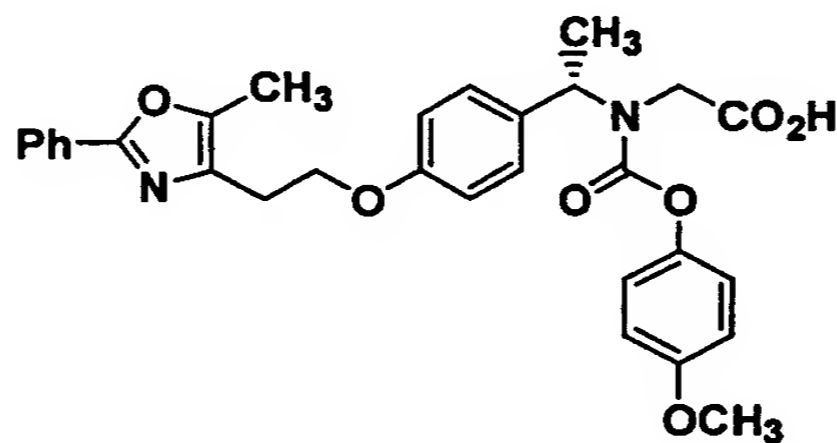


- 5 To a solution of Part C compound in MeCN (59 mL) were successively added K_2CO_3 (2.43 g; 17.6 mmol) and the mesylate (4.93 g; 17.6 mmol).



- 10 The reaction was heated at 90°C for 20 h, then cooled to RT. The mixture was partitioned between EtOAc and H_2O . The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; stepwise gradient from 8:1 to 3:1 to 1:1
15 hexane:EtOAc) to give Part D compound (3.4 g; 36%).

E.

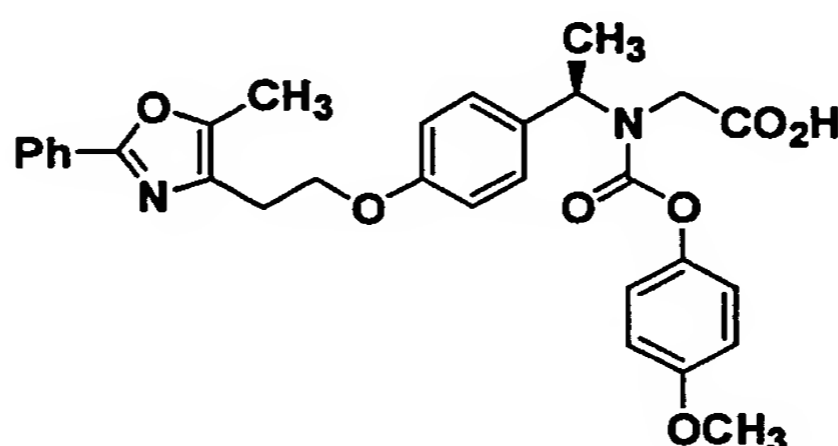


20

- To a solution of Part D compound (3.4 g; 6.25 mmol) in THF: H_2O (31 mL of a 2:1 solution) was added $LiOH \cdot H_2O$ (0.525 g; 125 mmol). The reaction was stirred at RT overnight for 14 h. EtOAc was added and the solution was
25 acidified with 1 N HCl solution to pH ~2. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow

rate = 25 mL/min; 22 min continuous gradient from 70:30 B:A to 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; retention time = 17.8 min) to give the title compound (2.1 g; 63% yield) as a white solid. [M + H]⁺ = 531.3; ¹H NMR (DMSO-d₆; 400 MHz): δ 1.50 (2d, J = 6.6 Hz; 3H), 2.37 (s, 3H), 2.94 (t, J = 7.0 Hz, 2H), 3.74 (s, 3H), 3.81 (m; 2H), 4.21 (t, J = 6.2 Hz, 2H), 5.36 (m, 1H), 6.93 (m, 6H), 7.28 (m, 2H), 7.50 (m, 3H), 7.91 (m, 2H)

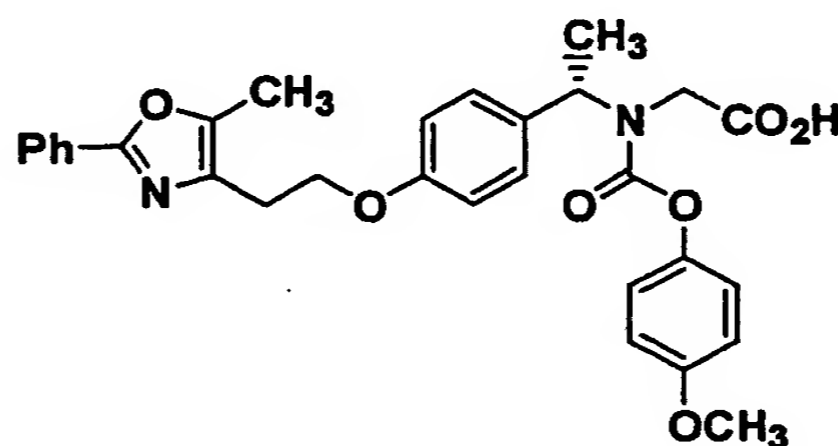
10

Example 499

15

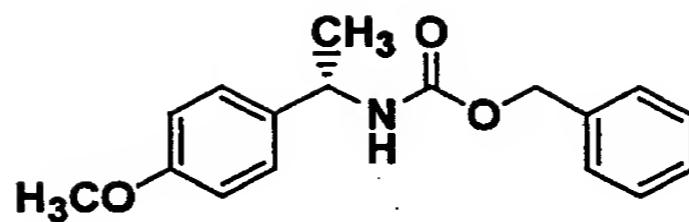
The synthesis of title compound was done using the identical sequence described for Example 498 compound except that (R)-4-methoxy-α-methyl benzylamine was used instead of the (S) isomer. [M + H]⁺ = 531.3;

¹H NMR (DMSO-d₆; 400 MHz): δ 1.50 (2d, J = 7.0 Hz; 3H), 2.37 (s, 3H), 2.94 (t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.84 (m; 2H), 4.21 (t, J = 6.6 Hz, 2H), 5.35 (m, 1H), 6.93 (m, 6H), 7.29 (m, 2H), 7.50 (m, 3H), 7.91 (m, 2H)

Alternative Synthesis of Examples 498 and 499Example 498A

30

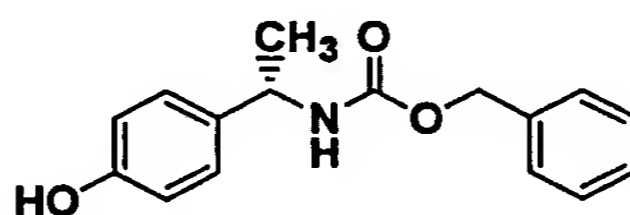
A.



To a RT mixture of (S)-1-(4-methoxyphenyl)-
5 ethylamine (5.45 g, 36 mmol) in THF (50 mL) and aqueous
NaHCO₃ (6.05g in 25 mL H₂O) was added dropwise benzyl
chloroformate (6.20 mL; 43 mmol). The reaction was
stirred at RT for 30 min; the organic phase was isolated
and concentrated in vacuo. The residue was partitioned
10 between EtOAc and H₂O (100 mL each); the organic phase was
washed with brine, dried (MgSO₄), and concentrated in
vacuo to about 30 mL volume. An equivalent volume of
hexane (30 mL) was added and Part A compound (9.12 g;
89%) crystallized as colorless needles.

15

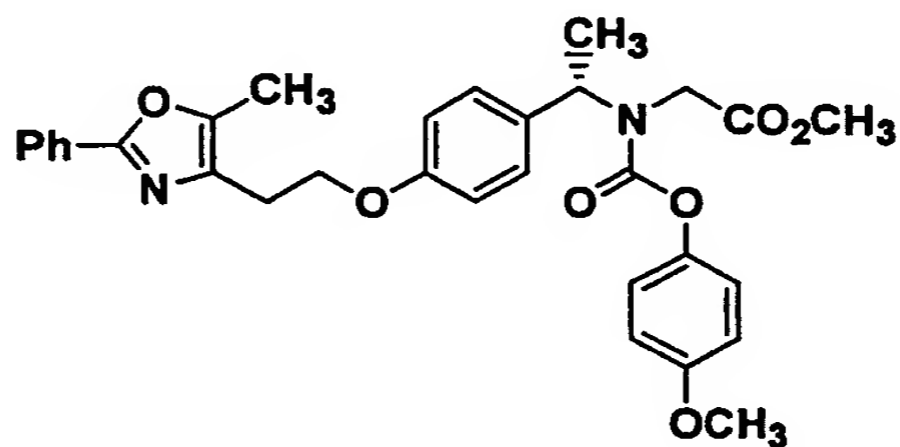
B.



To a -78°C solution of Part A compound (2.50 g; 8.8
20 mmol) in anhydrous CH₂Cl₂ (11 mL) was added dropwise a
solution of BBr₃ in CH₂Cl₂ (11.4 mL of a 1.0 M solution;
11.4 mmol) over 25 min. The reaction was allowed to warm
to 0°C and stirred at 0°C for 6 h, then quenched carefully
at -78°C by dropwise addition of excess MeOH (6 mL). The
25 solution was allowed to warm to 0°C and stirred at 0°C for
5 min. The solution was partitioned between CH₂Cl₂ (60
mL) and H₂O (50 mL). The organic phase was washed
successively with brine and 5% aqueous NaHCO₃ (50 mL
each), dried (MgSO₄) and concentrated in vacuo. The
30 residue was chromatographed (SiO₂; stepwise gradient from
4:1 to 1:1 hex:EtOAc) to furnish Part B compound (1.30 g;
63% yield based on 650 mg (26%) of recovered unreacted
Part A compound) as a white solid.

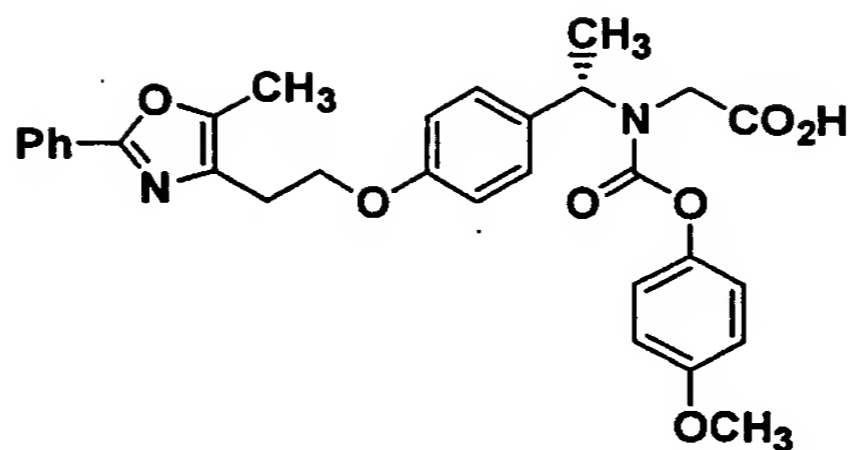
A solution of Part D compound (600 mg; 1.86 mmol), methyl bromoacetate (230 μ L; 2.42 mmol) and Et₃N (337 μ L; 2.42 mmol) in THF (10 mL) was stirred at RT for 20 h. The reaction mixture was partitioned between H₂O and EtOAc (60 mL) each. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from hex:EtOAc 4:1 to 1:1) to furnish Part E compound (640 mg; 87%) as an oil.

F.



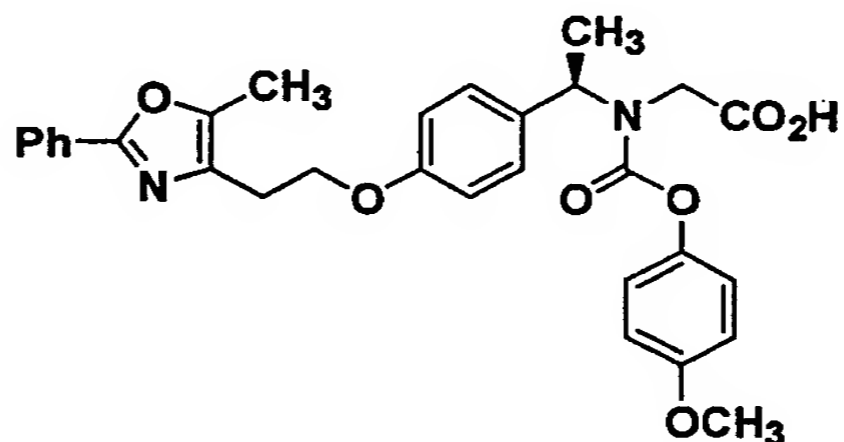
A solution of Part E compound (600 mg; 1.52 mmol), 4-methoxyphenyl chloroformate (271 μ L; 1.82 mmol) and DMAP (30 mg; 0.25 mmol) in pyridine (10 mL) was heated at 70°C for 2 h. Since starting material still remained at this point, additional 4-methoxyphenyl chloroformate (271 μ L; 1.82 mmol) was added and the reaction was heated at 70°C for an additional 1 h. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc (100 mL) and 1M aqueous HCl (60 mL). The organic phase was washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from hex:EtOAc 9:1 to 4:1) to furnish Part F compound (880 mg) as an oil.

G.



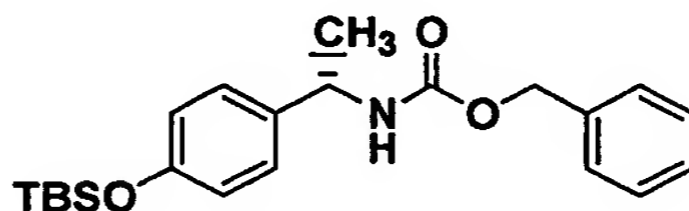
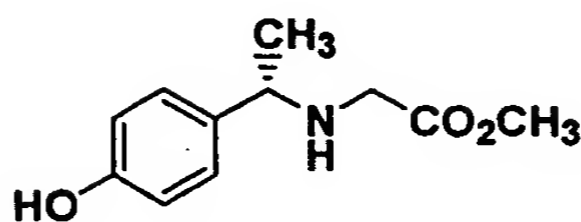
To a solution of Part F compound (880 mg; 1.62 mmol) in THF:H₂O (22 mL of a 2:1 solution) was added LiOH.H₂O (203 mg; 4.86 mmol). The reaction was stirred at RT for 18 h; then EtOAc (100 mL) was added and the solution acidified with 1 N HCl solution to pH 2. The organic phase was washed with water and brine (100 mL each), dried (MgSO₄) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 30 x 250 mm column; flow rate = 25 mL/min; 22 min continuous gradient from 70:30 B:A to 100% B + 5 min hold-time at 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; retention time = 17.8 min) and then lyophilized from dioxane to give the title compound (665 mg; 78%) as a white solid.

Example 499A

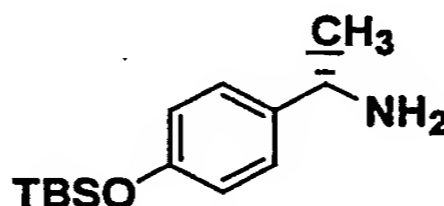


The alternative synthesis of Example 499 was done using the identical sequence described for Example 498A except that (R)-1-(4-methoxyphenyl)ethylamine was used instead of the (S) isomer.

5 A.

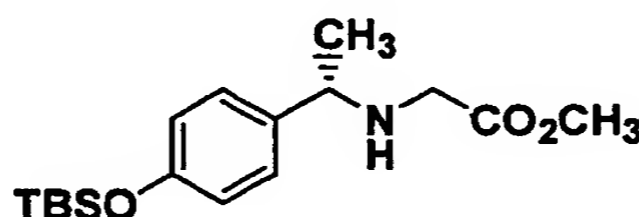


B.



30

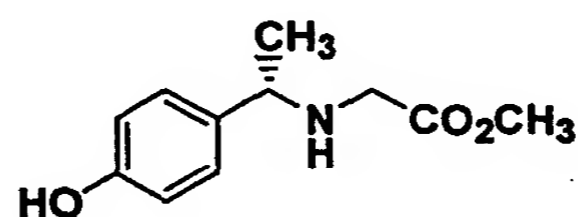
C.



A solution of Part B compound (230 mg), methyl bromoacetate (86 μ L; 0.91 mmol) and Et₃N (127 μ L; 0.91 mmol) in THF (10 mL) was stirred at RT for 15h. The reaction mixture was partitioned between H₂O and EtOAc (30 mL) each. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from hex:EtOAc 9:1 to 1:1) to furnish Part C compound (177 mg; 66% over 2 steps) as an oil.

10

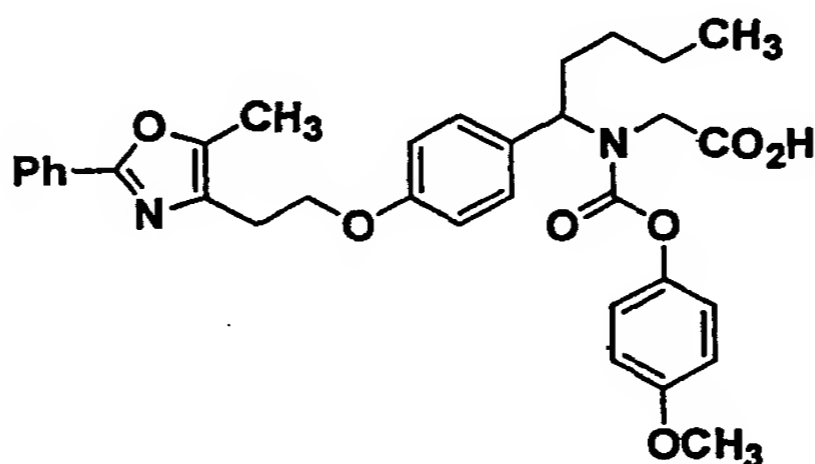
Example 498 Part B Compound



To a solution of Part C compound (177 mg; 0.55 mmol) in THF (5.5 mL) was slowly added tetrabutylammonium fluoride (1.65 mL of a 1 M solution in THF). The reaction was stirred at RT for 10 min, then partitioned between water and EtOAc. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 100% A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; retention time = 2.6 min) to provide the title compound (97 mg; 84%).

30

Example 500

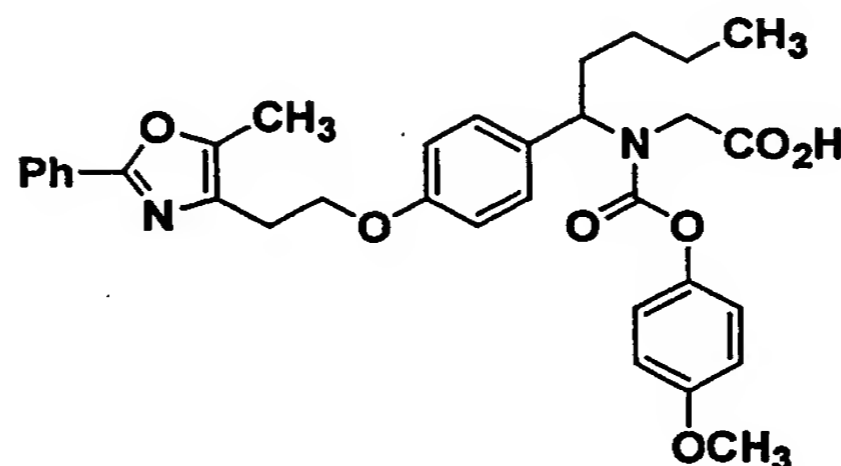


CCCC(=O)c1ccc(OCCc2c(C)c3c(c2)nc(c3)C4=CC=CC=C4)cc1CCOC(=O)N(CC)C(c1ccc(OCCc2c(C)c(O)c(Nc3ccccc3)c2)cc1)CC

A mixture of Part A compound (3.42 g; 9.42 mmol), glycine methyl ester HCl salt (1.18 g; 9.42 mmol), Et₃N (1.97 mL; 14.1 mmol), NaBH(OAc)₃ (2.80 g; 13.2 mmol) and HOAc (0.54 mL; 9.42 mmol) in DCE (20 mL) was stirred at
25 RT for 6 days. At this point the reaction was incomplete, but was not progressing any further. The reaction was quenched with saturated aqueous NaHCO₃ (6 mL), then concentrated in vacuo. The residue was partitioned between saturated aqueous NaHCO₃ and EtOAc.
30 The organic phase was washed with saturated aqueous NaHCO₃ and H₂O, then extracted with 1M aqueous HCl (the unreacted starting material remained in the organic phase). The aqueous phase was basified with NaOH, then extracted with EtOAc. The organic phase was washed with H₂O and brine,

dried (MgSO_4) and concentrated in vacuo to give Part B compound (365 mg; 9%) as an oil.

C.

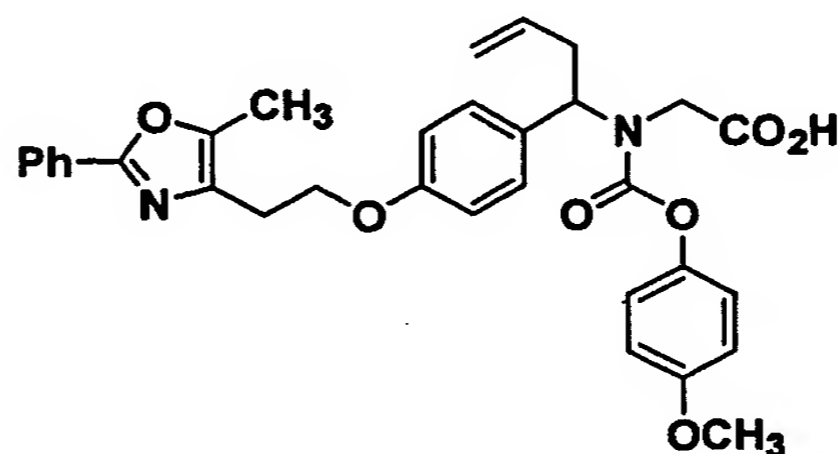


5

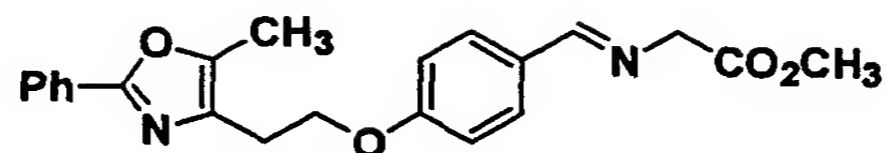
To a solution of Part C compound (50 mg; 0.11 mmol) in pyridine (1 mL) was added 4-methoxyphenyl chloroformate (40 μL) and DMAP (5 mg). The reaction mixture was heated at 60°C for 6 h, then was cooled to RT and volatiles were removed in vacuo. The residue was dissolved in THF/MeOH/ H_2O (1 mL of a 2:2:1 mixture) and LiOH (30 mg) was added. The reaction was stirred at RT for 18 h, then was acidified with aqueous 1 M HCl to pH ~ 2. The mixture was extracted with EtOAc (30 mL), washed with H_2O and brine (15 mL each), dried (MgSO_4) and concentrated in vacuo to give the crude product. This material was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; continuous gradient from 60:40 A:B to 100% B over 30 min) to give, after lyophilization from MeOH/ H_2O , the title compound (52 mg; 79%) as a white solid. $[\text{M} + \text{H}]^+ = 573.3$

25

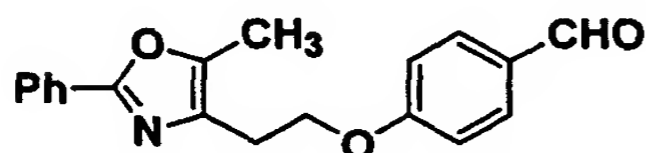
Example 501



A.



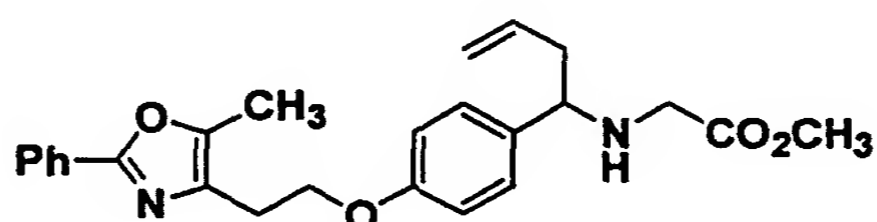
5 A mixture of glycine methyl ester hydrochloride (245 mg; 1.95 mmol), Et₃N (271 μ L; 1.95 mmol) and the aldehyde



10 (400 mg; 1.3 mmol) and anhydrous MgSO₄ (200 mg) in THF (4 mL) was stirred at RT overnight, then filtered. The filtrate was concentrated in vacuo to give crude Part A compound, which was used in the next step without further purification.

15

B.

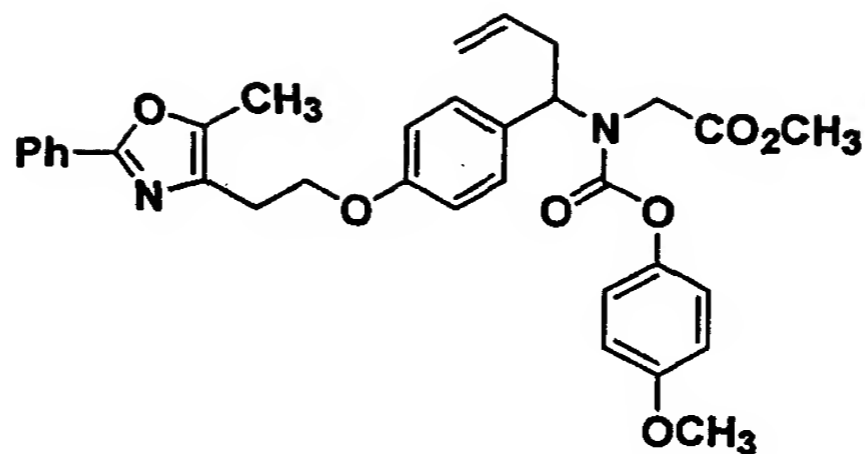


20 A mixture of indium metal (448 mg; 3.9 mmol) and allyl bromide (334 μ L; 3.9 mmol) in anhydrous DMF (2 mL) was stirred at 0°C for 50 min. A solution of the crude Part A compound (from above) in anhydrous DMF (2 mL) was added to this mixture, and the reaction was stirred

25 vigorously at RT for 3 h. Analytical HPLC/MS showed that the reaction was complete at this point. The reaction was partitioned between saturated aqueous NH₄Cl and EtOAc. The organic phase was washed with H₂O (an emulsion formed) and brine, dried (MgSO₄) and concentrated in vacuo to give

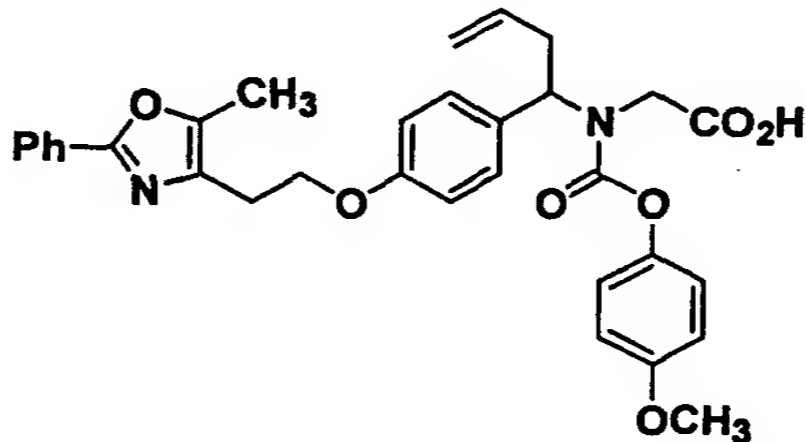
30 crude Part B compound (300 mg; 55% for 2 steps). This material was used in the next step without further purification.

C.



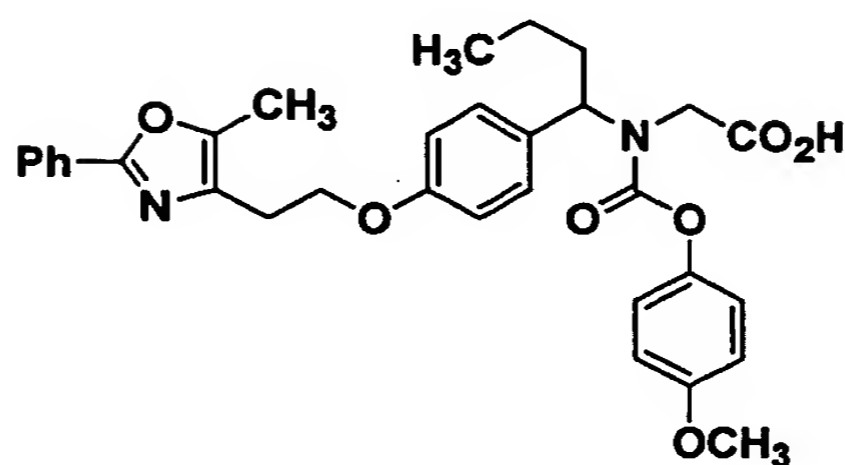
5 To a 0°C solution of Part B compound (150 mg; 0.36 mmol) and Et₃N (51 µL; 0.36 mmol) in CH₂Cl₂ (4 mL) was added dropwise 4-methoxyphenyl chloroformate (53 µL; 0.36 mmol). The reaction was allowed to warm to RT and stirred at RT for 1 h, then concentrated in vacuo. The
10 residue was chromatographed (SiO₂; hexane:EtOAc 2:1) to give Part C compound (200 mg; 98%) as an oil.

D.



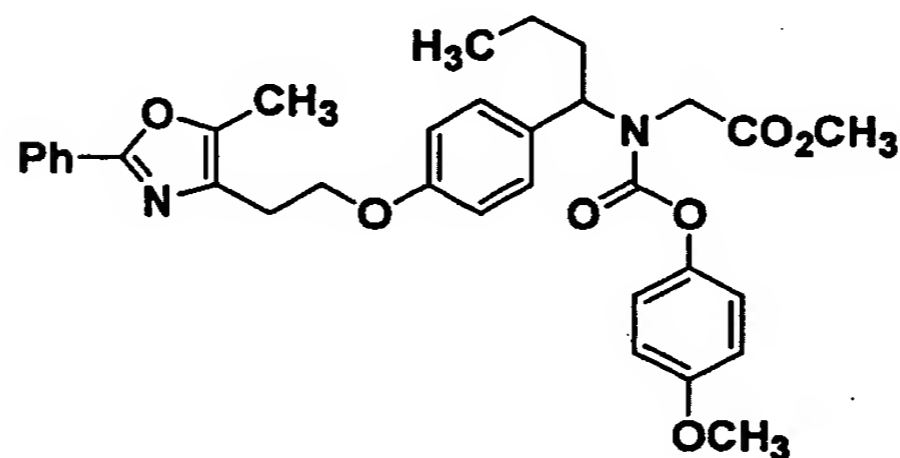
15

A solution of Part C compound (100 mg, 0.18 mmol) and LiOH·H₂O (30 mg, 0.72 mmol) in THF:MeOH:H₂O (1 mL of a 1:1:1 solution) was stirred at RT for 2 h. The reaction
20 mixture was then acidified to pH ~ 2 with aqueous 1N HCl. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried (Na₂SO₄), concentrated in vacuo and lyophilized from dioxane to provide title compound (80 mg; 82%) as a white solid.
25 [M + H]⁺ = 557.2

Example 502

5

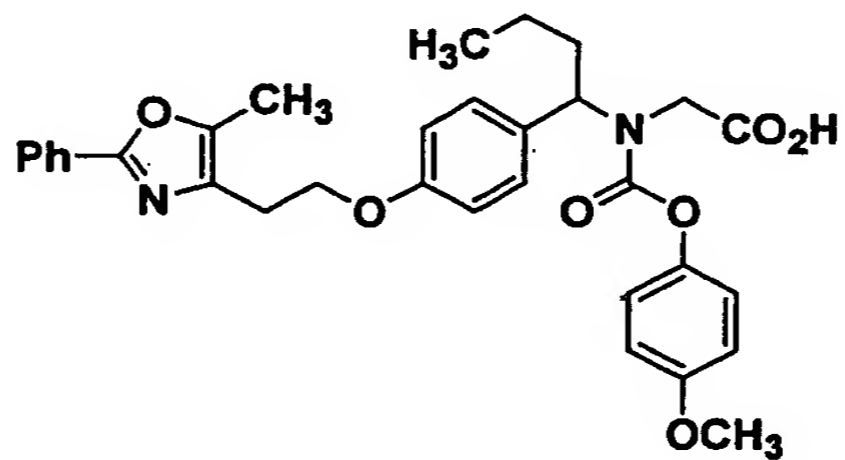
A.



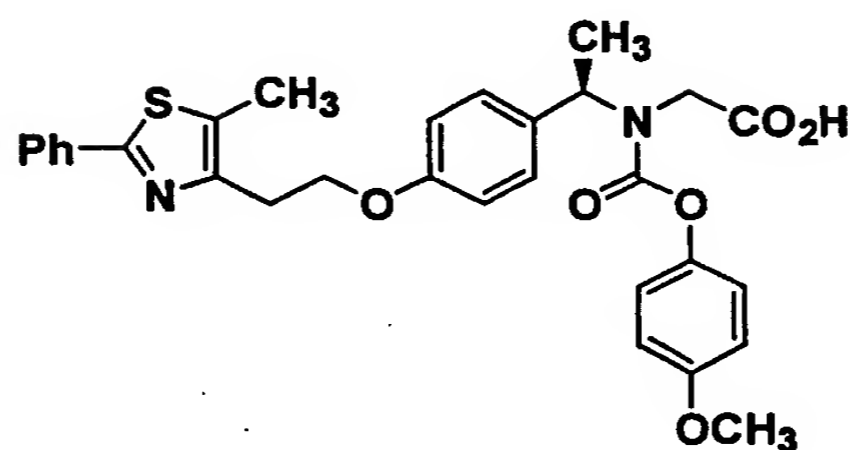
A solution of Example 501 Part C compound (100 mg;
10 0.18 mmol) in MeOH (10 mL) in the presence of 10% Pd/C
(50 mg) was stirred under an H₂ atmosphere for 2 h at RT.
The catalyst was then filtered off using a pad of
Celite[®]. The filtrate was concentrated in vacuo to give
Part A compound (100 mg; 100%) as an oil.

15

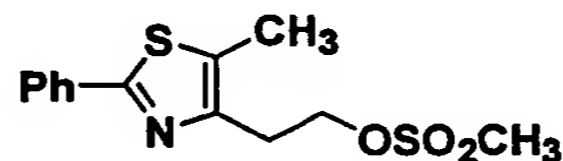
B.



20 Title compound (87 mg; 90%; white solid lyophilate)
was obtained from Part A compound in the same way as
Example 501 compound was synthesized from Example 501
Part C compound. [M + H]⁺ = 559.2

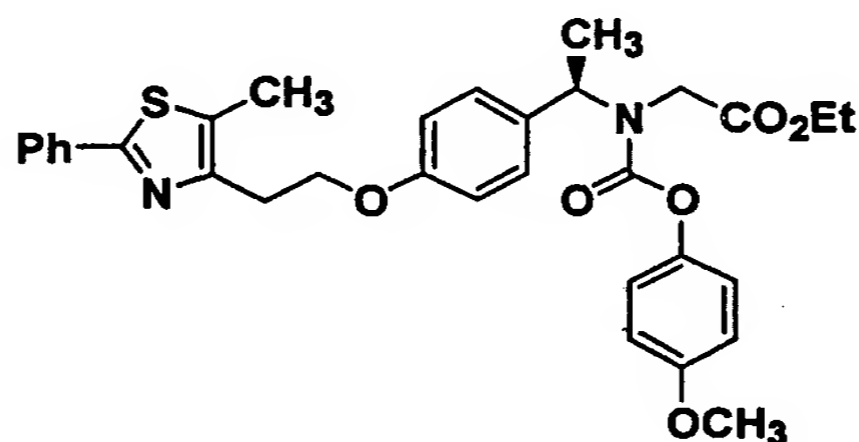
Example 503

5 A.

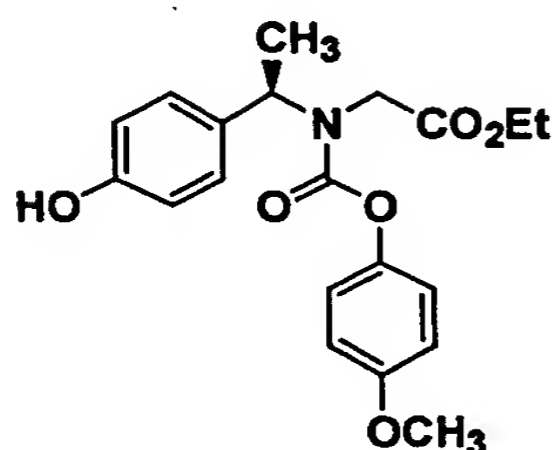


To a solution of 5-methyl 2-phenyl-thiazol-4-yl-
10 ethanol (50 mg; 0.23 mmol) in CH_2Cl_2 (3 mL) were
successively added Et_3N (50 μL ; 0.36 mmol) and
methanesulfonyl chloride (20 μL ; 0.26 mmol). The
reaction was stirred at RT for 2 h, then was partitioned
between CH_2Cl_2 and aqueous 1 M HCl. The organic phase was
15 washed with brine, dried (Na_2SO_4), and concentrated in
vacuo to give Part A compound (68 mg; 100%) as a
colorless oil. This material was used in the next step
without further purification.

20 B.



A mixture of the phenol (prepared using the
25 identical procedures as described for the synthesis of
Example 498 Part C compound except that ethyl
bromoacetate was used instead of methyl bromoacetate)

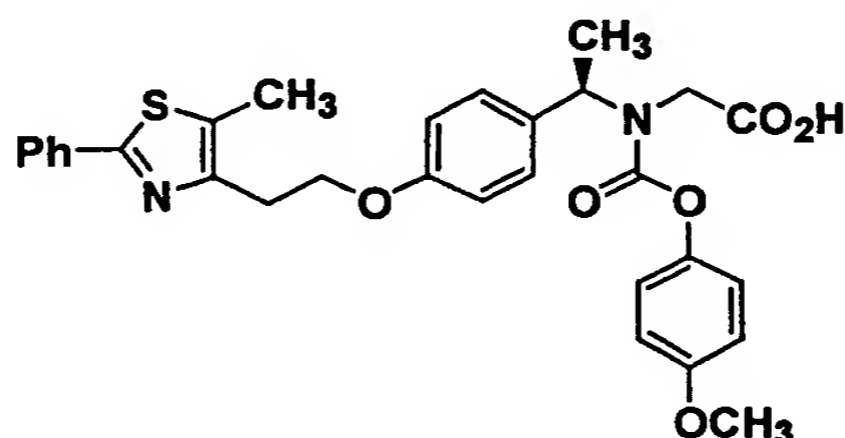


(18 mg; 0.048 mmol) and K_2CO_3 (30 mg; 0.22 mol) in MeCN (2 mL) was heated at 60°C overnight, then cooled to RT and partitioned between EtOAc and excess aqueous 1 M HCl.

- 5 The aqueous phase was extracted with EtOAc (2x); the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 498) to provide Part B compound (12 mg; 43%).

10

C.



- 15 A solution of Part B compound (12 mg; 0.02 mmol) and LiOH.H₂O (10 mg; 0.24 mmol) in THF (2 mL) and H₂O (1 mL) was stirred at RT for 4 h. The reaction mixture was acidified with excess aqueous 1 M HCl and extracted with EtOAc (3x). The combined organic extracts were dried
- 20 (Na_2SO_4) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 498) to give the title compound (3 mg; 26%) as a colorless oil. $[M + H]^+ = 547.2$

CC1=C(C=C(C=C1)C2=CC=CC=C2)CCOC3=CC=C(C=C3)C(=O)N(C)C(C)C(=O)OC4=CC=C(C=C4)OCCCOC(=O)CN(C)C(=O)C(C)C1=CC=C(O)C=C1C2=CC=C(OC)C=C2

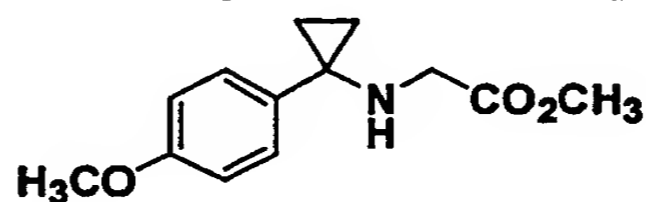
10

CC1=C(CCOc2ccc(cc2)C3(C3)N(CCO)C(=O)Oc4ccc(OC)cc4)C(=O)N1c5ccccc5COC1=CC=C(C2(C)C)C=C1N2

- 245 -

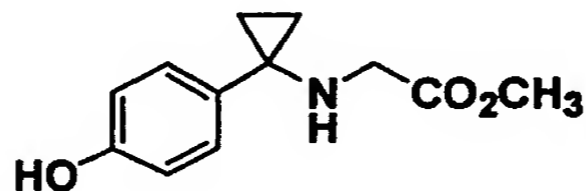
Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and H₂O. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to give the crude product (presumably the corresponding isocyanate). This material was dissolved in aqueous 8 M HCl (1.8 mL), stirred at RT for 5 min, then heated to 100°C for 1 h. After cooling to RT, Et₂O was added, and the solution was cautiously basified with excess solid NaOH. The aqueous phase was extracted with Et₂O (3 x 15 mL), dried (MgSO₄) and concentrated in vacuo to provide compound A (100 mg; 47%) as an oil. This material was used in the next step without further purification.

B.



A solution of Part A Compound (100 mg; 0.61 mmol), methyl bromoacetate (103 mg; 0.67 mmol) and Et₃N (102 µL; 0.73 mmol) in THF was stirred at RT for 16 h. The reaction mixture was partitioned between EtOAc and H₂O. The organic phase was washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed (SiO₂; CH₂Cl₂:MeOH 9:1) to give Part B compound (90 mg; 62%) as an oil.

C.

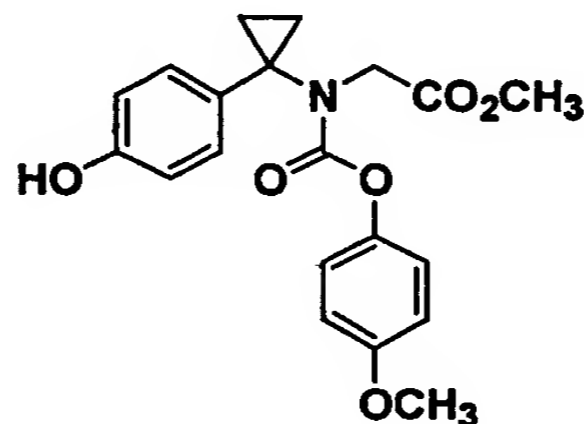


30

To a 0°C solution of Part B compound (90 mg; 0.38 mmol) in CH₂Cl₂ (12.7 mL) was slowly added neat BBr₃ (82 µL; 0.87 mmol). The reaction was stirred at 0°C for 3 h, then was partitioned between ice cold saturated aqueous

NH₄Cl and EtOAc. The organic phase was discarded and the aqueous layer was neutralized by addition of NaHCO₃, then extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo to give Part C compound (50 mg; 59%).

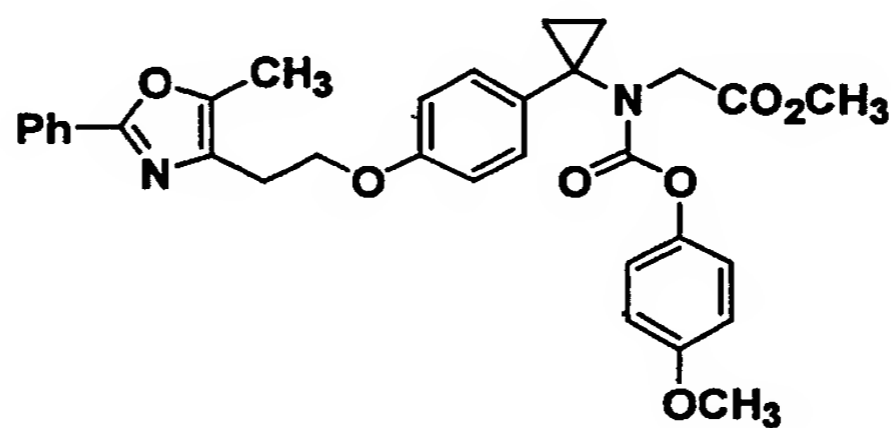
D.



10

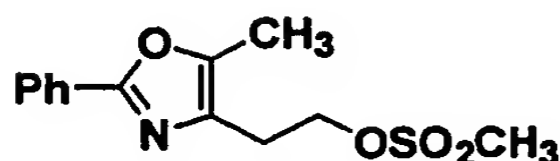
A mixture of Part C compound (50 mg; 0.22 mmol), 4-methoxyphenyl chloroformate (33 mg; 0.22 mol) and NaHCO₃ (25 mg; 0.29 mmol) in 1:1 aqueous dioxane (7.5 mL) was stirred at RT for 2 h. The reaction mixture was partitioned between EtOAc and H₂O. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo to give Part D compound (45 mg; 52%).

E.



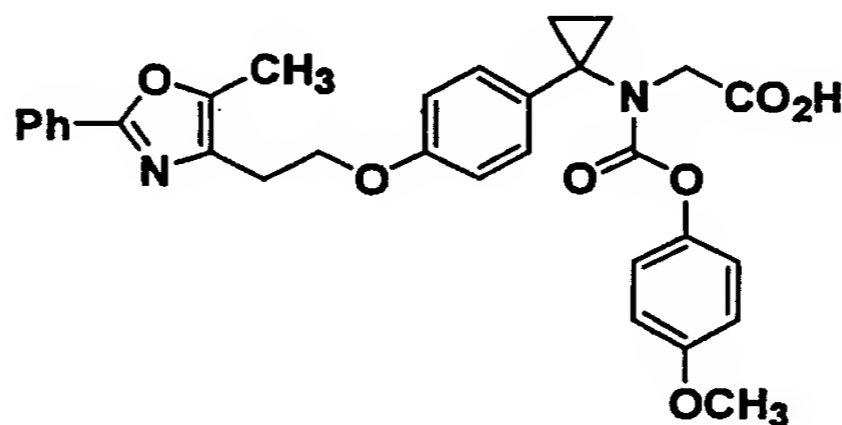
20

A mixture of Part D compound (45 mg; 0.12 mmol), K₂CO₃ (30 mg; 0.22 mol) and the mesylate (33 mg; 0.12 mmol)



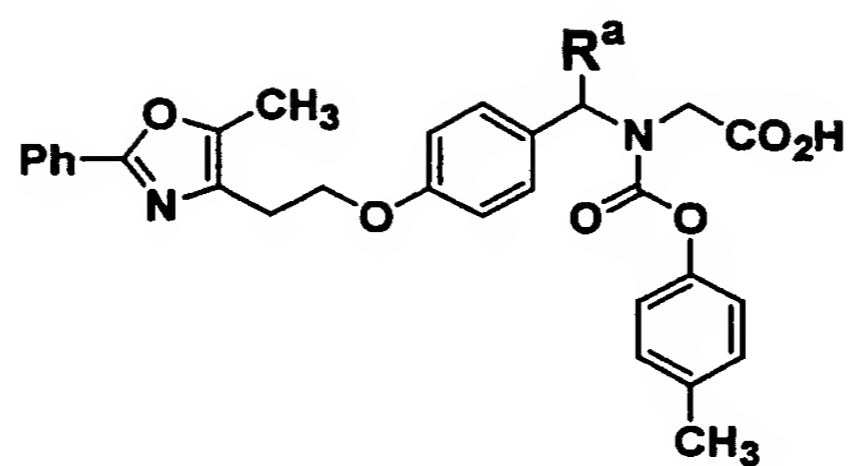
5

10



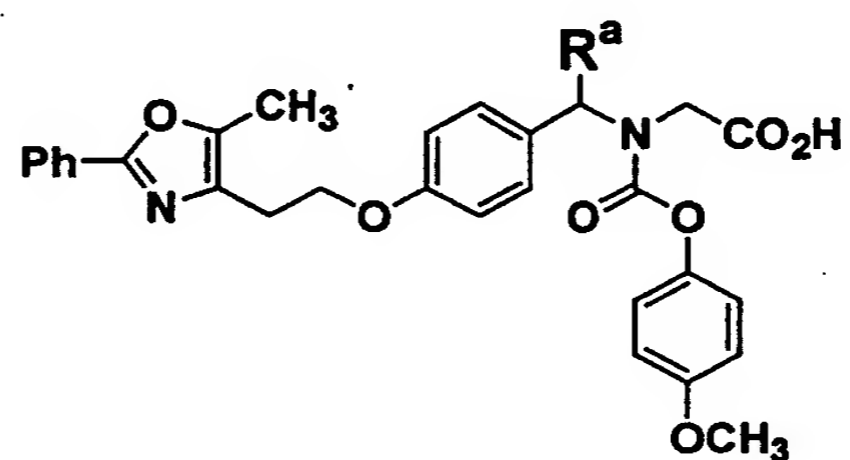
15

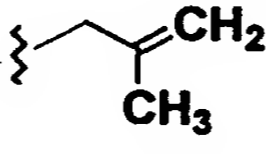
Example 498) to give the title compound (28 mg; 68%) as a colorless oil. $[M + H]^+ = 543.2$



Example No.	R ^a	[M+H] ⁺
506	(±) -Me	515.3
507	(±) n-Bu	557.4

5



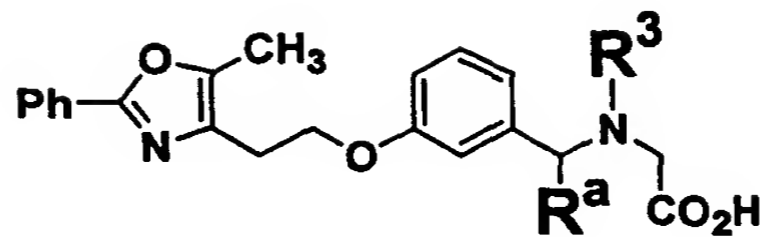
Example No.	R ^a	[M+H] ⁺
508	(±) Me	531.3
509	(±) Et	545.1
510	(±) i-Bu	573.3
511	(±) 	571.3

CC1=CC=C(C=C1)C2=C(C)OC(=N2)CCCOc3ccc(cc3)C(C)C(=O)Oc4ccc(C)cc4C(=O)O

¹H NMR (DMSO-d₆; 400 MHz): δ 1.47 and 1.54 (2d, J = 7.5 Hz; 3H), 2.29 (s, 3H), 2.37 (s, 3H), 2.93 (t, J = 6.6 Hz, 2H), 3.81 (2d, J = 18 Hz; 2H), 4.21 (t, J = 6.6 Hz, 2H), 5.3 (m, 1H), 6.94 (m, 4H), 7.18 (d, J = 8.4 Hz, 2H), 7.31 (m, 2H), 7.49 (m, 2H)

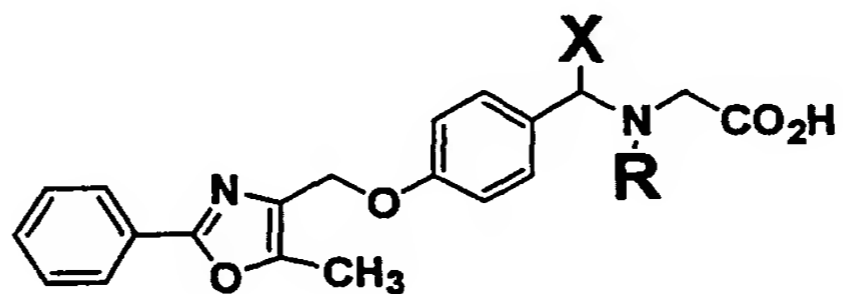
CC1=C(C=C(C=C1C2=CC=CC=C2)OC3=CC=CC=C3)N=C(C=C3C(=C(C=C(C=C3)C)OC4=CC=CC=C4)C(=O)N(C)CC(=O)O)O5=CC=C(C=C5)OC

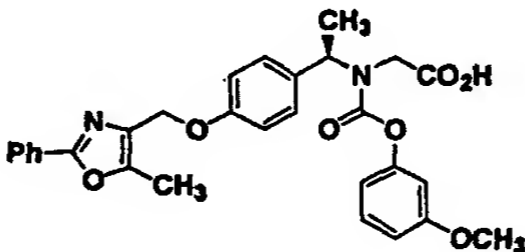
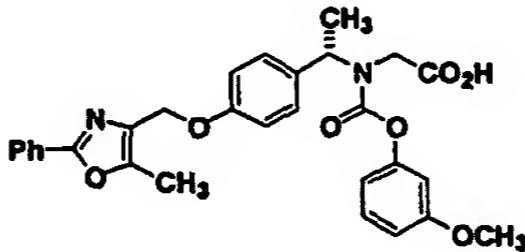
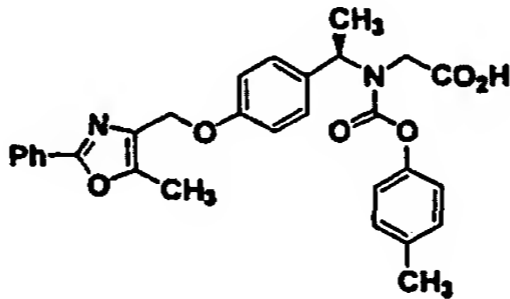
¹H NMR (DMSO-d₆; 400 MHz): δ 1.47 and 1.54 (2d, J = 7.5 Hz; 3H), 2.37 (s, 3H), 2.94 (t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.81 (m, 2H), 4.21 (t, J = 6.6 Hz, 2H), 5.36 (m, 1H), 6.94 (m, 4H), 7.29 (m, 2H), 7.49 (m, 3H), 7.91 (m, 2H)



Example No.	Structure	[M+H] ⁺
512	<p>(±)</p>	531.3

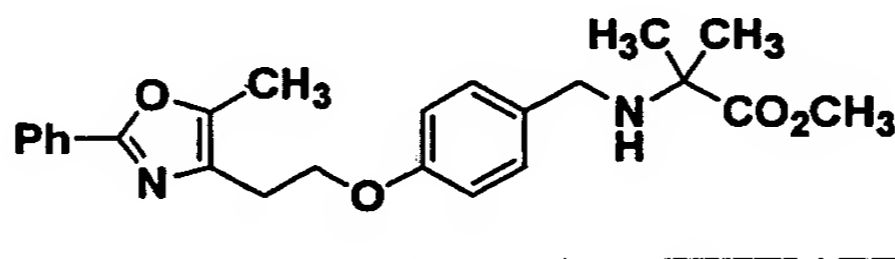
5 The synthesis of Examples 513-518 involved the use
of Example 541 Part B compound as the alkylating agent.



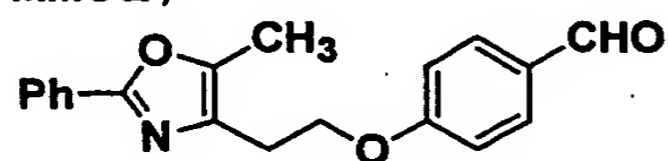
Example No.	Structure	[M+H] ⁺
513		517.2
514		517.2
515		501.2

5

A.

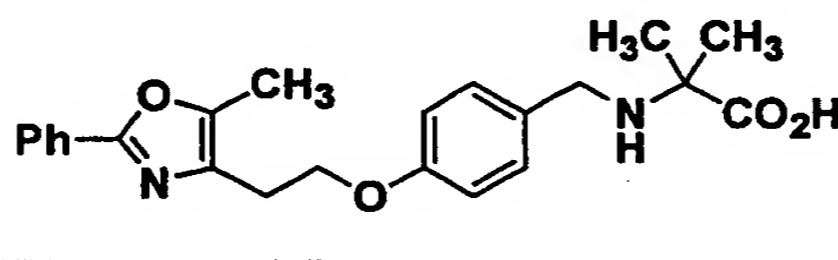


A mixture of methyl α -aminoisobutyrate hydrochloride (108 mg; 0.7 mmol), Et₃N (146 μ L; 111 mmol), NaBH(OAc)₃ (222 mg; 11 mmol) and the aldehyde (215 mg; 07 mmol)



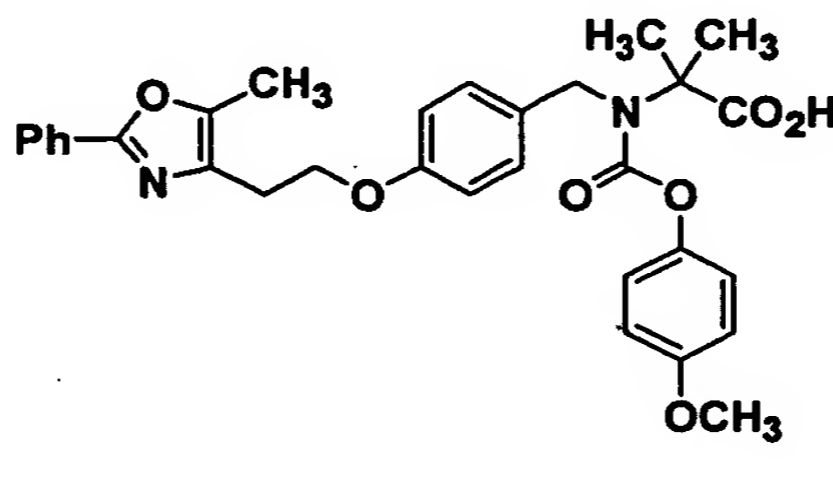
in DCE (5 mL) was stirred at RT for 21 h. Some starting material remained, so the reaction was heated at 55°C for 4 h (no further reaction). Saturated aqueous NaHCO₃ was added, and volatiles were removed in vacuo. The residue was partitioned between H₂O and EtOAc. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed with brine and extracted with aqueous 1 M HCl. The aqueous phase was basified with solid NaOH and extracted with EtOAc (2x). The organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give crude Part A compound (174 mg; 61%).

B.



A solution of Part A compound (120 mg; 0.29 mmol) aqueous LiOH (2.0 mL of a 0.3 M solution of a 1:1:1 mixture of THF:MeOH:H₂O) was stirred at RT overnight. The reaction was acidified to pH ~ 2 with aqueous 1 M HCl, then was concentrated in vacuo and purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; continuous gradient from 40:60 B:A to 100% B over 30 min, where solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA) to furnish Part B compound (60 mg; 53%) as a syrup.

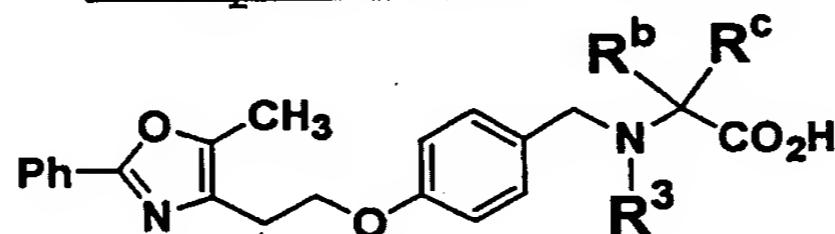
C.



A solution of Part B compound (25 mg; 0.06 mmol), 4-methoxyphenyl chloroformate (20 μ L) in pyridine (1 mL) was heated at 60°C for 6 h. Volatiles were removed in vacuo and the residue was partitioned between EtOAc (2 mL) and aqueous 1 M HCl (1 mL). The organic phase was concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; continuous gradient from 40:60 B:A to 100% B over 20 min, where solvent A = 90:10:0.1 H₂O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H₂O:TFA) to furnish title compound (4 mg; 12%) as a white foam. $[M + H]^+ = 545.3$

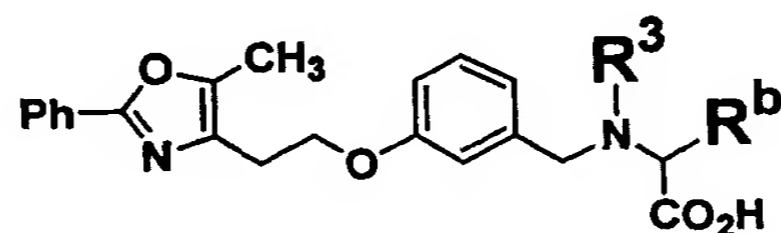
Following the procedures as set out hereinbefore, the following Examples 520 to 535 compounds were prepared.

Examples 520 to 535



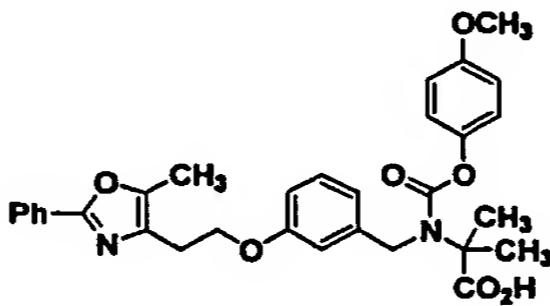
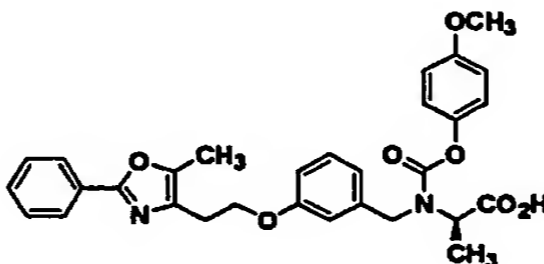
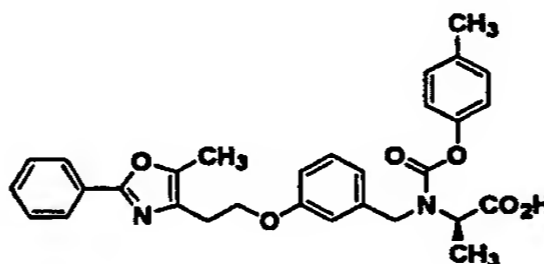
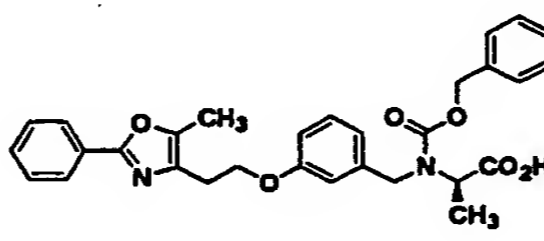
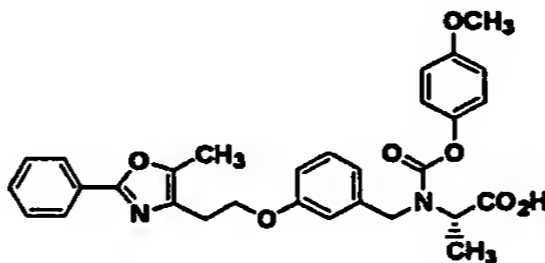
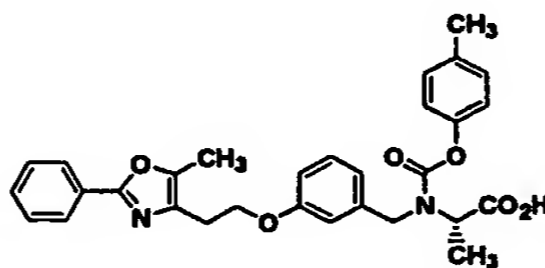
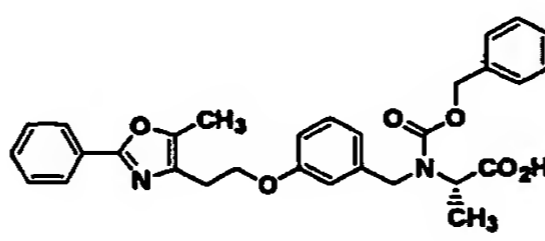
Example No.	Structure	$[M+H]^+$
520		543.4
521		527.3
522		531.2
523		515.2

Exempl No.	Structure	[M+H] ⁺
524		531.2
525		515.2
526		515.2

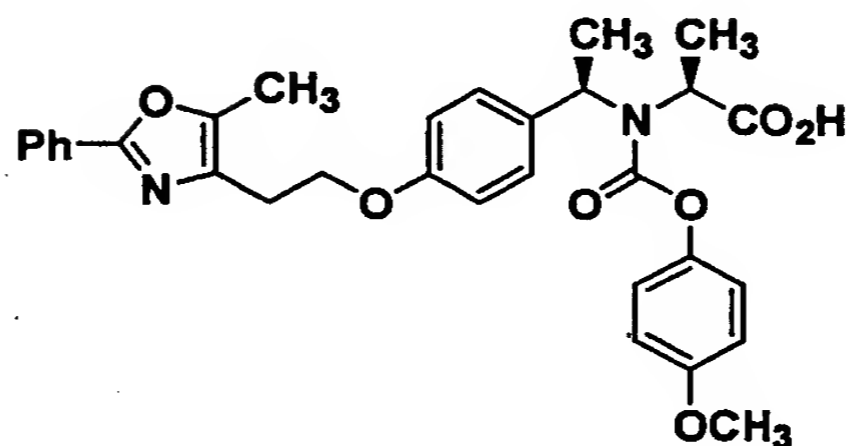


5

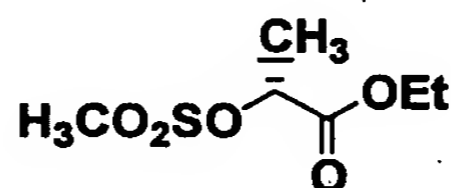
Example No.	Structure	[M+H] ⁺
527		543.3
528		527.3

529		545.3
530		531.2
531		515.2
532		515.2
533		531.2
534		515.2
535		515.2

Example 536

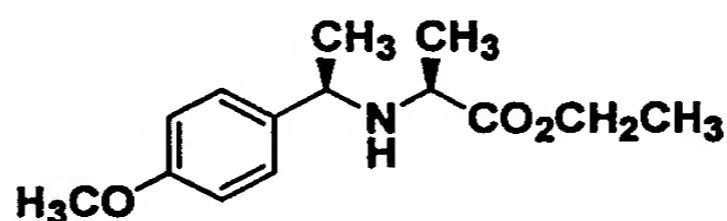


A.



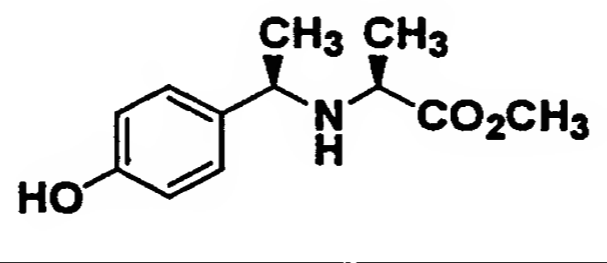
10 To a 0°C solution of (R)-(-)-lactate (3.0 g; 29 mmol) and Et₃N (4.8 mL; 35 mmol) in CH₂Cl₂ (60 mL) was added methanesulfonyl chloride (2.67 mL; 35 mmol). The mixture was stirred at 0°C for 1 h, then partitioned between CH₂Cl₂ and 1M aqueous HCl (100 mL each). The organic phase was washed with H₂O and brine, dried (MgSO₄), and concentrated in vacuo without heating to give Part A compound as an oil (4.5 g; 86%), which was used in the next step without further purification.

B.



A mixture of Part A compound (1.42 g; 6.0 mmol),
25 (R)-4-methoxy- α -methyl benzylamine (300 mg, 2.0 mmol),
and K_2CO_3 (828 mg; 6.0 mmol) in MeCN (20 mL) was heated at
70°C for 17 h (some amine starting material still
remained). The reaction cooled to RT, filtered, and the
volatiles were removed in vacuo. The residue was
30 partitioned between EtOAc and H_2O . The organic phase was
washed with brine, dried ($MgSO_4$), and concentrated in

5 C.

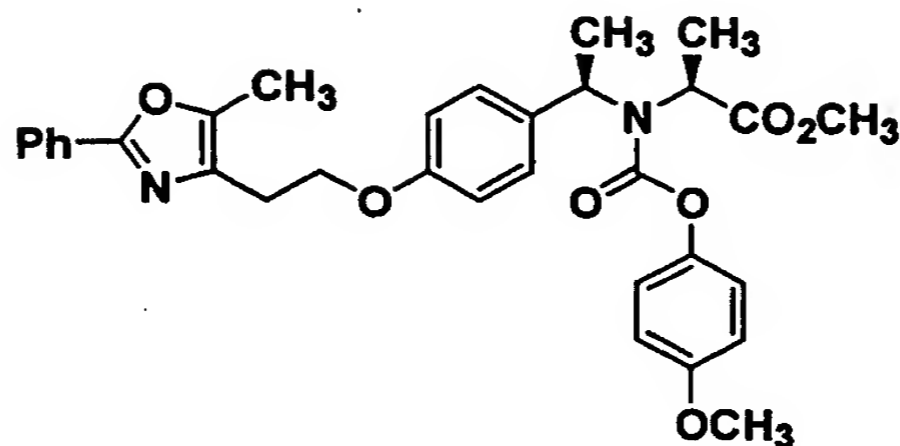


20

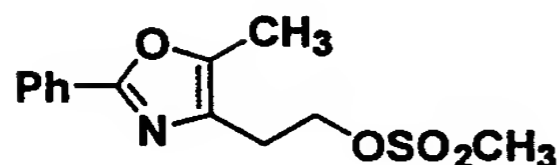
COC(=O)C(C)N(C(=O)Oc1ccc(OC)cc1)C(c1ccc(O)cc1)C

30

E.

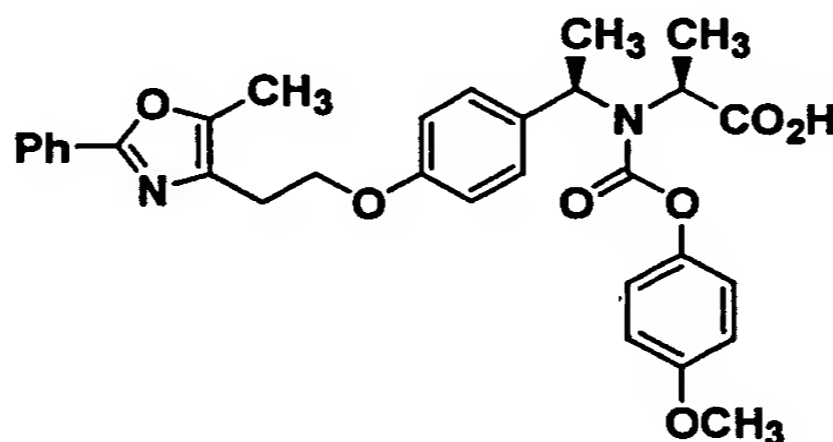


To a solution of Part D compound (330 mg; 0.88 mmol) in MeCN (20 mL) were successively added K_2CO_3 (165 mg; 1.2 mmol) and the mesylate (337 mg; 1.2 mmol).



The reaction mixture was heated at 95°C for 16 h, then cooled to RT and filtered. The filtrate was concentrated in vacuo and then partitioned between EtOAc and H₂O. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; 3:1 hexane:EtOAc) to give Part E compound (350 mg; 71%).

F.

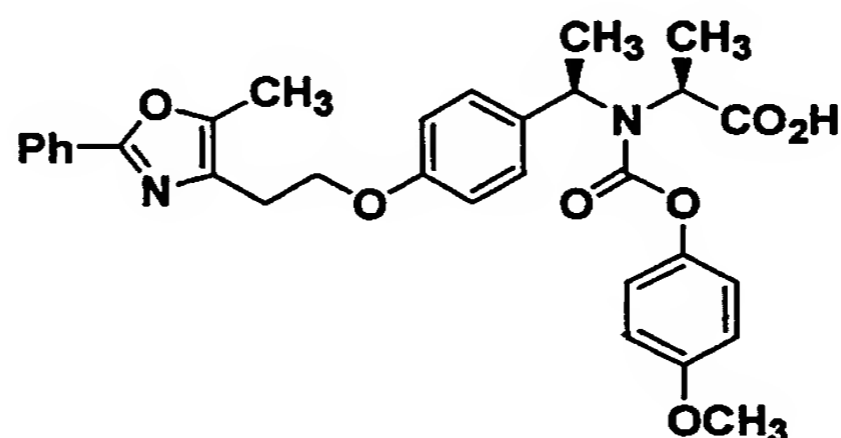


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solution acidified with 1 N HCl solution to pH ~ 2. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; 20 min continuous gradient from 50:50 B:A to 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; retention time = 26 min) and lyophilized from dioxane to give the title compound (208 mg; 61% yield) as a white solid.

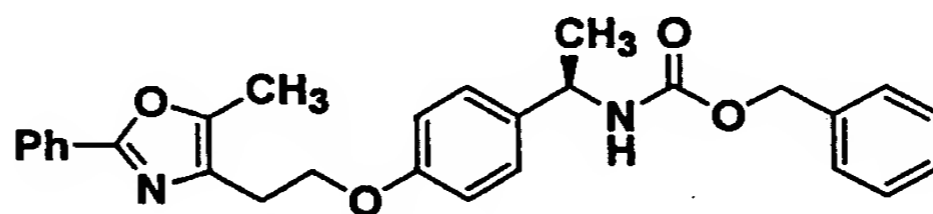
10 [M + H]⁺ = 545.3

Alternative Synthesis of Example 536:

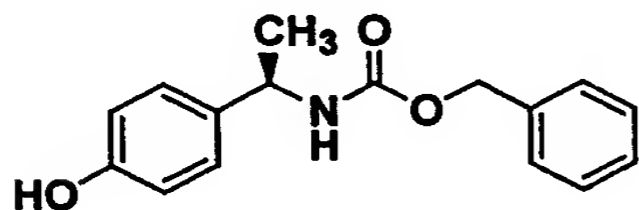


15

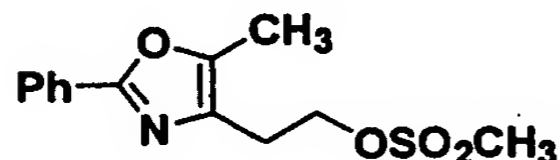
A.



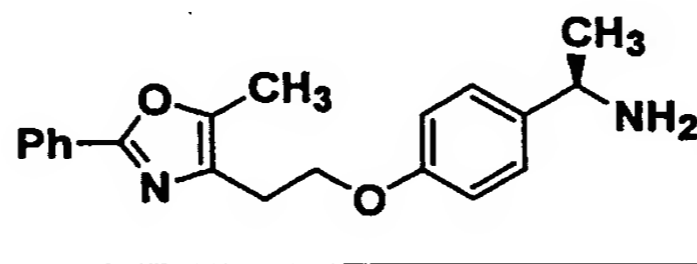
A mixture of the phenol [500 mg; 1.94 mmol; prepared from (R)-1-(4-methoxyphenyl)ethylamine as for the alternative synthesis of Example 498],



25 K₂CO₃ (400 mg; 2.89 mmol) and the mesylate (710 mg; 2.52 mmol)

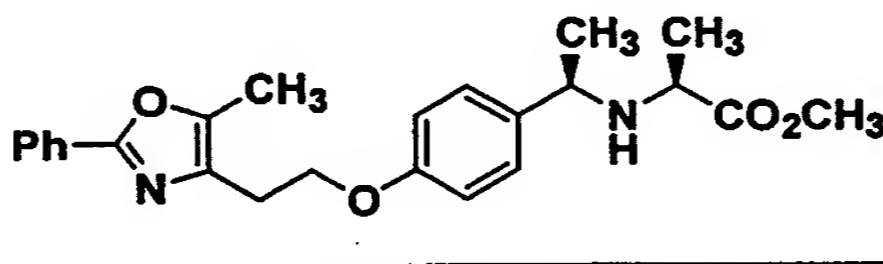


10 B.

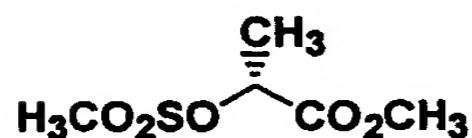


A mixture of Part A compound (300 mg; 0.66 mmol) and 10% palladium on carbon (50 mg) in MeOH (20 mL) was stirred under an atmosphere of H₂ (balloon) at RT for 2 h, at which point the reaction was complete by HPLC. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo to provide Part B compound (208 mg; 79%) as an oil which eventually became a white solid upon standing.

C.



25 A mixture of Part B compound (160 mg; 0.50 mmol), K_2CO_3 (206 mg; 1.49 mmol) and the mesylate (292 mg; 1.49 mmol; Example 536 Part A compound)



30

in MeCN (5 mL) was heated at 70°C for 24 h. At this point more mesylate (97 mg; 0.50 mmol) was added, and the reaction was heated at 70°C for a further 16 h. The reaction mixture was cooled to RT and filtered. The

filtrate was concentrated in vacuo, and the residue was chromatographed (SiO₂; stepwise gradient from hex:EtOAc 3:1 to 1:1) to furnish Part C compound (98 mg; 47%) as an oil. This intermediate was then used for the preparation of Example 536 in an identical manner to that previously shown.

Examples 537 to 539

10 Following the procedures set out hereinbefore, the Examples 537 to 539 compounds were prepared.

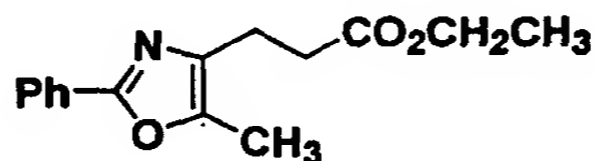
Example No.	Structure	[M+H] ⁺
537		545.3
538		545.3
539		545.3

Example 540

Cc1c(C#N)cc2c1oc(c2)c3ccccc3

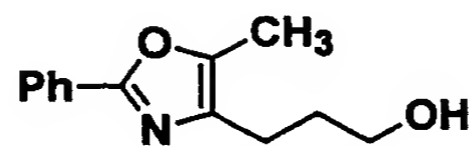
15

20

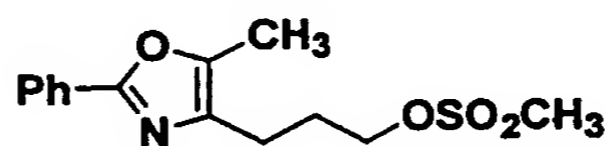


25

C.

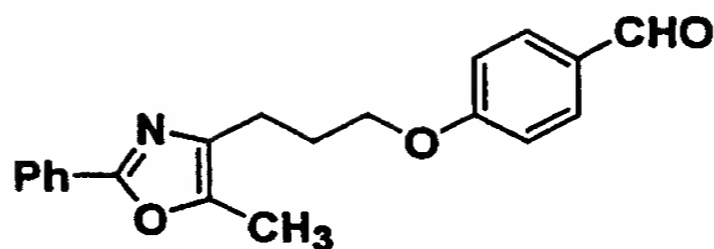


D.



- 264 -

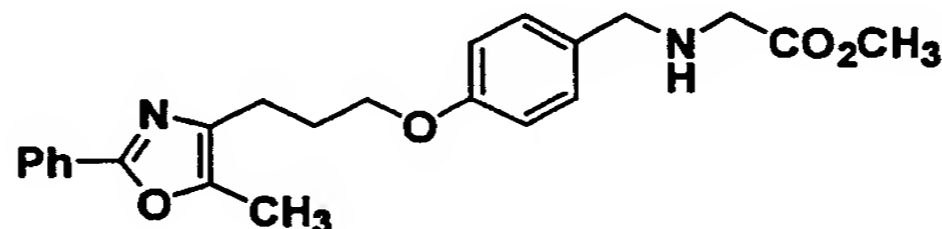
E.



A mixture of Part D compound (380 mg; 1.29 mmol),
5 4-hydroxybenzaldehyde (188 mg; 1.55 mmol) and K_2CO_3 (214
mg; 1.55 mmol) in MeCN (12 mL) was refluxed in an oil bath
for 17 h. At this point all starting Part D compound had
been consumed (but there was a significant quantity of
the hydrolysis by-product, Part C compound) by HPLC/MS.
10 The reaction was cooled to RT and the solid precipitates
were filtered off. The filtrate was concentrated in
vacuo and partitioned between EtOAc (60 mL) and H_2O (40
mL). The organic phase was washed with brine (40 mL),
dried ($MgSO_4$), and concentrated in vacuo to give the crude
15 product. This material was chromatographed (SiO_2 ;
stepwise gradient from 4:1 to 1:2 hex:EtOAc) to give Part
E compound (150 mg; 36%) as an oil in addition to Part C
compound (100 mg; 36%).

20

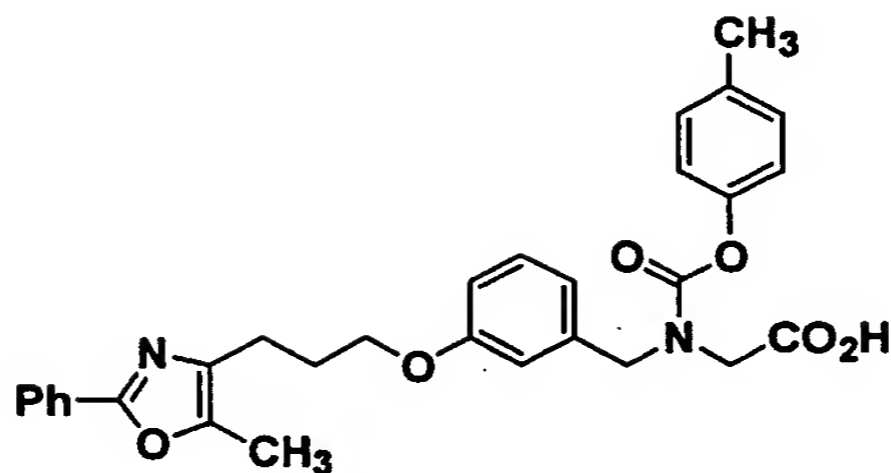
F.



A mixture of Part E compound (150 mg; 0.50 mmol),
25 glycine methyl ester hydrochloride (75 mg; 0.60 mmol) and
 Et_3N (84 μL ; 0.60 mmol) in MeOH (5 mL) was stirred at RT
for 6 h, after which $NaBH_4$ (50 mg) was added cautiously
portionwise. The reaction mixture was stirred at RT
overnight, after which volatiles were removed in vacuo.
30 The residue was partitioned between EtOAc and H_2O . The
organic phase was washed with brine, dried (Na_2SO_4) and

concentrated in vacuo to give Part F compound (180 mg; 97%) as an oil.

G.

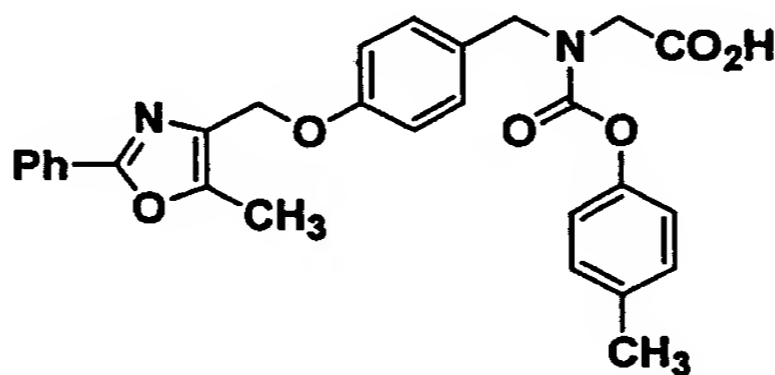


5

A mixture of Part F compound (23 mg; 0.060 mmol), Et₃N (10 μ L; 0.66 mmol) and 4-tolyl chloroformate (10 μ L; 0.066 mmol) in CH₂Cl₂ (1 mL) was stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was dissolved in a solution of THF/MeOH/H₂O (1 mL of a 2:2:1 mixture); LiOH.H₂O (14 mg; 0.33 mmol) was added, and the reaction was stirred at RT for 2 h. Volatiles were removed in vacuo, and the residue was partitioned between aqueous 1 M HCl and EtOAc. The organic extract was concentrated in vacuo and the residue was purified by preparative HPLC (YMC ODS S5 30 mm x 250 mm column, continuous 25 minute gradient from 40% B:60% A to 100% B, hold at 100% B for 15 min, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; flow rate = 25 mL/min) to give the title compound as a white solid (13 mg; 45% over 2 steps). [M + H]⁺ = 515.3

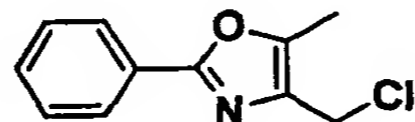
25

Example 541

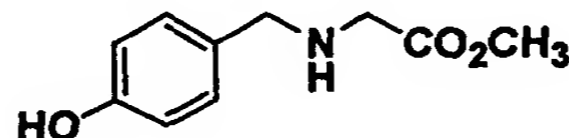


Cc1c(C)c2c(c1)oc(c2)c3ccccc3

B.



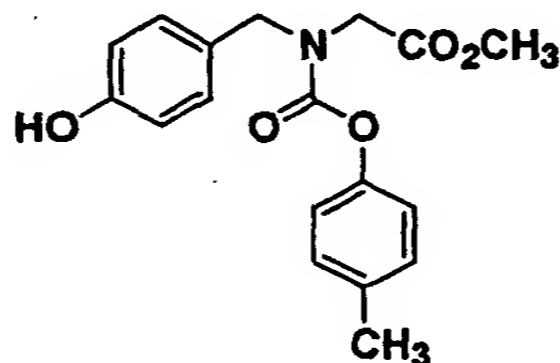
C.



- 267 -

while maintaining the reaction temperature at <RT. The reaction mixture was stirred for 5 h, then was concentrated in vacuo to give crude Part C compound, which was used in the next step without further purification.

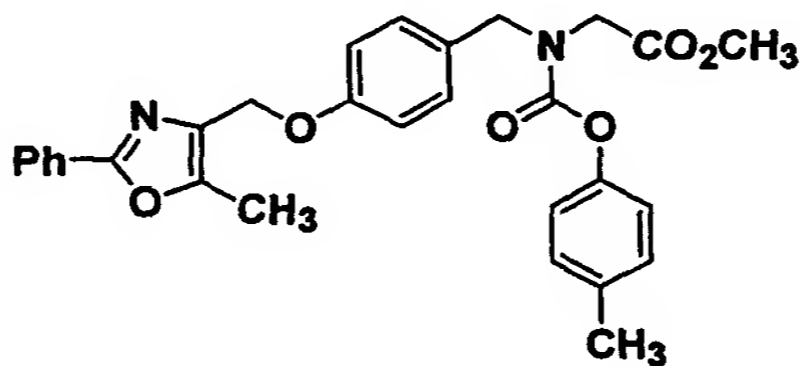
D.



10

To a solution of crude Part C compound in Et₂O (300 mL) and H₂O (200 mL) were added NaHCO₃ (20 g, 240 mmol, in a single portion) and 4-tolyl chloroformate (15 mL, 150 mmol; dropwise). The biphasic reaction mixture was stirred for 12 h at RT. The aqueous phase was then extracted with Et₂O (2 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from 3:1 to 1:1 hexane:EtOAc) to give Part D compound (40.8 g; 76% over 2 steps) as an oil.

E.



25

A solution of Part B compound (14.5 g, 70 mmol), Part C compound (21.6 g, 67 mmol) and K₂CO₃ (18.4 g, 134 mmol) in CH₃CN (150 mL) was stirred at 80°C for 12 h. The reaction was cooled to RT and volatiles were removed in vacuo. The brown oily residue was partitioned between

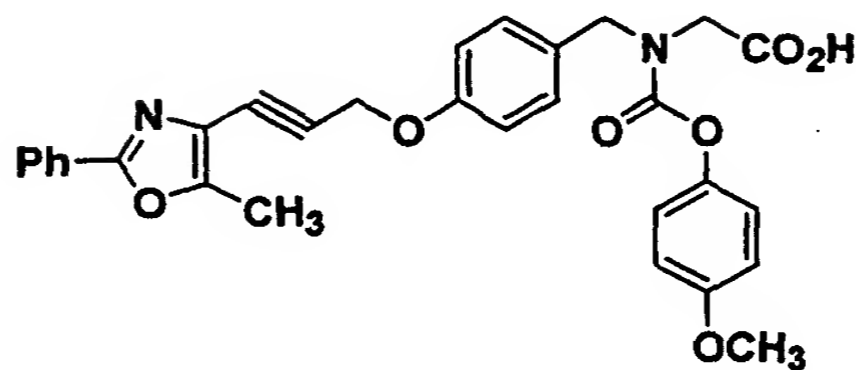
5

CC1=C(C(=C(C=C1)OCc2c(C)nc(C3=CC=CC=C3)oc2)COC(=O)NCC(=O)O)C=C(C=C3)C=C(C=C3)C

15

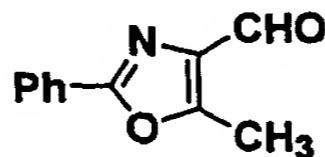
25

30

Example 542

5

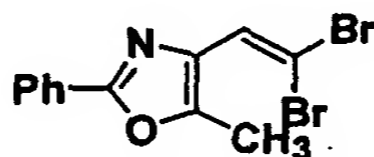
A.



A mixture of 2-phenyl-5-methyl-oxazole-4-acetic
 10 acid (470 mg; 2.17 mmol; Maybridge) pyridine N-oxide (830
 mg; 8.74 mmol) and acetic anhydride (350 mg; 3.57 mmol)
 in toluene (10 mL) was heated at 90°C for 12 h, then
 concentrated in vacuo. The residue was then partitioned
 between EtOAc and 1M aqueous HCl. The organic phase was
 15 washed with saturated aqueous NaHCO₃, brine, dried
 (Na₂SO₄) and concentrated in vacuo to give a dark brown
 oil. This material was chromatographed (SiO₂; 4:1
 hex:EtOAc) to give Part A compound (143 mg; 35%) as an
 oil.

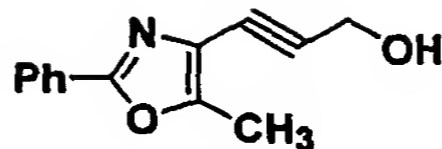
20

B.



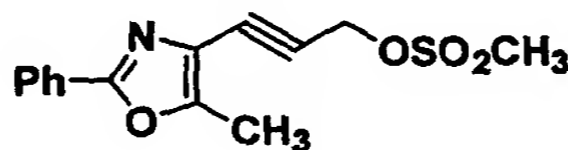
25 To a 0°C solution of Part A compound (600 mg; 3.21
 mmol) and Ph₃P (3.37 g; 12.9 mmol) in CH₂Cl₂ (50 mL) was
 added dropwise a solution of CBr₄ (2.13 g; 6.4 mmol) in
 CH₂Cl₂ (20 mL). The solution was stirred at 0°C for 2 h,
 then allowed to warm to RT and stirred at RT overnight.
 30 Volatiles were removed in vacuo and the residue was
 chromatographed (85:15 hexane:EtOAc) to furnish Part B
 compound (1.08 g; 98%) as a pale yellow solid.

C.



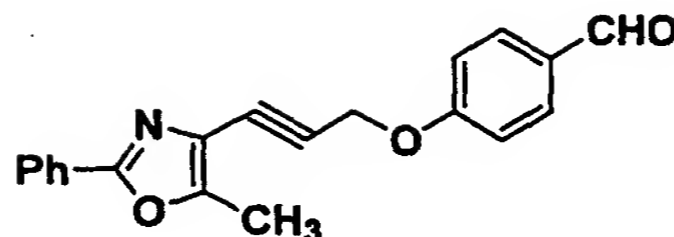
5 To a -78°C solution of Part B compound (1.12 g; 3.26 mmol) in THF (60 mL) was added n-butyllithium dropwise (4.2 mL of a 1.6 M solution in hexane; 6.72 mmol) over 25 min, while maintaining the internal temperature at $\leq -71^{\circ}\text{C}$. The reaction was stirred at -78°C for 1 h, then allowed to warm slowly to 0°C . Paraformaldehyde (305 g) was then added in one portion and the reaction was stirred at 0°C for 3 h and then quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with EtOAc (2x); the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give a dark oil. This material was chromatographed (SiO_2 ; 3:2 hex:EtOAc) to give Part C compound (466 mg; 67%) as a yellow solid.

20 D.



To a 0°C solution of Part C compound (466 mg; 2.19 mmol) and Et_3N in CH_2Cl_2 was added dropwise methanesulfonyl chloride (190 μL ; 2.45 mmol) and the reaction was stirred at 0°C for 1 h. The mixture was then partitioned between CH_2Cl_2 and cold 1M aqueous HCl . The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was chromatographed (SiO_2 ; 3:2 hex:EtOAc) to give Part D compound (533 mg; 84%) as an off-white solid.

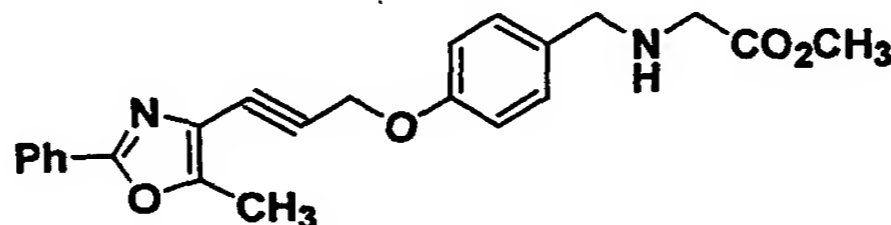
E.



5 A mixture of Part D compound (198 mg; 0.68 mmol),
4-hydroxybenzaldehyde (96 mg; 0.79 mmol) and K_2CO_3 (141
mg; 1.02 mmol) in CH_3CN (13 mL) was heated at $70^\circ C$ for
3 h, then stirred at RT overnight. Volatiles were
removed in vacuo, and the residue was partitioned between
10 EtOAc and 1 M aqueous NaOH. The organic phase was washed
with brine, dried (Na_2SO_4) and concentrated in vacuo to
give crude Part E compound (190 mg; 88%) as a yellow oil,
which was used in the next step without further
purification.

15

F.



20 A mixture of Part E compound (123 mg; 0.39 mmol),
glycine methyl ester hydrochloride (248 mg; 1.98 mmol)
and Et_3N (600 μL ; 4.3 mmol) in DCE (15 mL) was stirred at
RT for 15 min, after which $NaBH(OAc)_3 \cdot H$ (262 mg; 1.2 mmol)
was added in one portion. The reaction was stirred for
25 16 h at RT, after which additional $NaBH(OAc)_3 \cdot H$ (200 mg;
0.94 mmol) was added. Stirring was continued for 3 h,
after which still more $NaBH(OAc)_3 \cdot H$ (200 mg; 0.94 mmol) was
added. The reaction was stirred at RT for 48 h, after
which all Part E compound had been consumed. The
30 reaction mixture was partitioned between CH_2Cl_2 and
aqueous $NaHCO_3$. The aqueous phase was extracted with
 CH_2Cl_2 (2x). The combined organic extracts were washed
with brine, dried (Na_2SO_4) and concentrated in vacuo. The
crude product was chromatographed (SiO_2 ; stepwise gradient

5

COC(=O)CN(C(=O)Oc1ccc(OC)cc1)Cc2ccc(OCC#CC3=C(C)OC(=N3)c4ccccc4)cc2

20

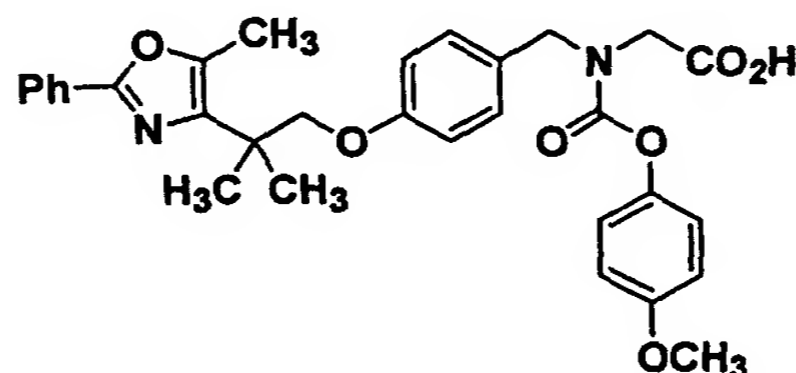
Cc1c(C#CCOCC2=CC=CC=C2C(=O)N(C)C(=O)OC3=CC=C(OC)C=C3)c4c(c1)oc(c45C6=CC=CC=C65)nc3ccccc3

30

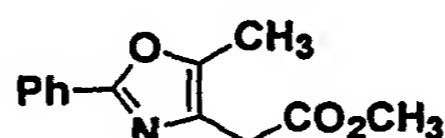
where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA) to give title compound (160 mg; 71%) as a white solid. $[M + H]^+ = 527.2$

5

Example 543

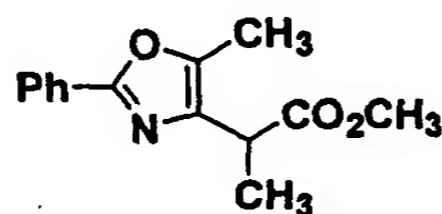


A.



A solution of 5-methyl-2-phenyloxazole-4-yl-acetic acid (4.0 g; 18 mmol) and concentrated HCl (2 mL) in MeOH (60 mL) was heated at reflux overnight. Volatiles were removed in vacuo; the residue was partitioned between H₂O and EtOAc. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo to give crude Part A compound as a colorless oil (4.00 g; 94%) which was used in the next step without further purification.

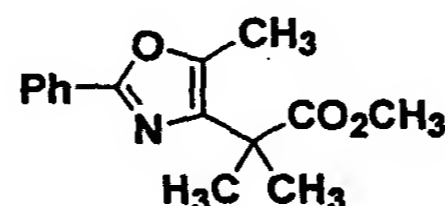
B.



25

To a -78°C solution of LDA (15.0 mL of a 2.0 M solution in heptane/THF; 30 mmol; Aldrich) were successively added dropwise a solution of Part A compound (2.3 g; 10 mmol) in THF (6 mL) and HMPA (500 μL ; 2.9 mmol). The solution was stirred at -78°C for 30 min, after which methyl iodide (1.87 mL; 30 mmol) was added dropwise. The solution was stirred at -78°C for 1 h,

10 C.



30

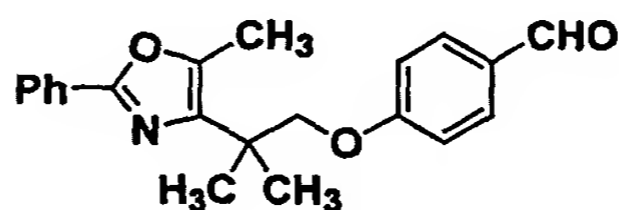
D.



To a -78°C solution of Part C compound (1.2 g; 4.63 mmol) in THF (3 mL) under an atmosphere of N_2 was added dropwise a solution of LiAlH_4 (1.0 mL of a 1.0 M solution in THF). The reaction was stirred at -78°C for 1 h, then
5 was allowed to warm to 0°C and stirred at 0°C for 30 min. The reaction was quenched by cautious addition of 1M aqueous potassium sodium tartrate followed by H_2O . The aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O , dried (MgSO_4) and
10 concentrated in vacuo to give crude Part D compound (1.01 g; 94%) as an oil, which was used in the next step without further purification.

E.

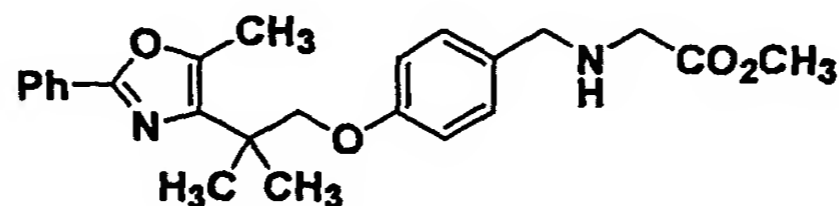
15



To an 80°C solution of Part D compound (700 mg; 3.0 mmol), Ph_3P (1.2 g; 4.6 mmol) and 4-hydroxybenzaldehyde
20 (406 mg; 3.3 mmol) in THF (10 mL) was added DEAD (720 μL ; mmol) in two portions over 5 min. The solution was stirred at 80°C for 1 h (starting material still remained), then was concentrated in vacuo. The residue
25 was chromatographed (SiO_2 ; stepwise gradient from 9:1 to 5:1 hexane:EtOAc) to give Part E compound (160 mg; 16%).

F.

30



A solution of Part E compound (250 mg; 0.75 mmol), glycine methyl ester hydrochloride (141 mg; 1.13 mmol) and Et_3N (157 μL ; 1.13 mmol) in MeOH (30 mL) was stirred at RT overnight. Excess solid NaBH_4 was added cautiously;
35 the reaction was stirred at RT for 1 h, then concentrated

5

COC(=O)CN(Cc1ccc(Oc2c(C)(C)c3c(C)c(Cn3c4ccccc4o2)cc1)cc1)C(=O)c3ccc(OC)cc3

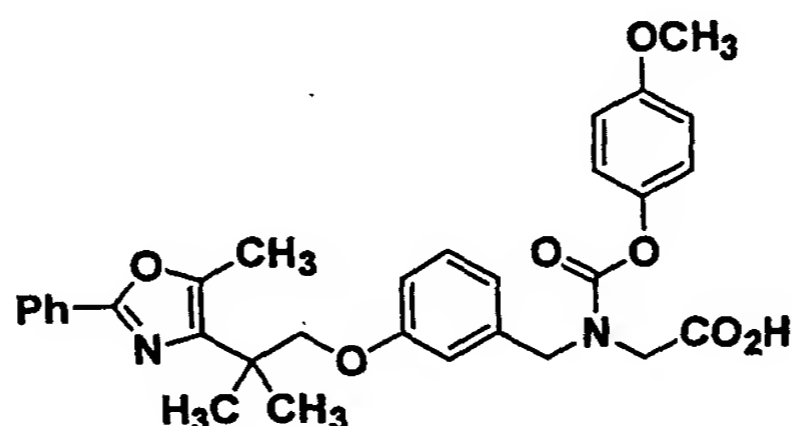
To a 0°C solution of Part F compound (150 mg; 0.37 mmol) and Et₃N (51 µL; 0.37 mmol) in CH₂Cl₂ (5 mL) was added 4-methoxyphenyl chloroformate (55 µL; 0.37 mmol). The reaction was allowed to warm to RT and stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was chromatographed (SiO₂; 5:1 hexane:EtOAc) to furnish Part G compound (130 mg; 63%).

CC1=C(C(C1)c2ccccc2)C(C)COc3ccc(cc3)C(=O)N(C)C(=O)Oc4ccc(OC)cc4C(=O)O

A solution of Part G compound (130 mg) and LiOH.H₂O (39 mg) in H₂O/THF/MeOH (2 mL of a 1:2:2 mixture) was stirred at RT for 2 h. Volatiles were removed in vacuo, and the residue was acidified with 1.0 M aqueous HCl, then extracted with EtOAc. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to give a residue, which was purified by preparative HPLC (YMC S5 ODS reverse phase C18, 30 x 250 mm column; flow rate = 25

5

Example 544

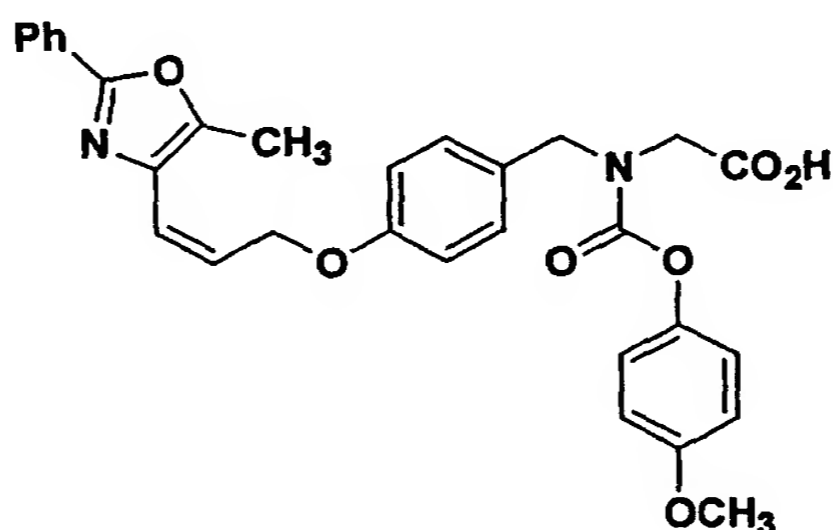


10

Example 543 except that 3-hydroxybenzaldehyde was used instead of 4-hydroxybenzaldehyde (in the preparation of Example 543 Part E compound). $[M + H]^+ = 545.4$

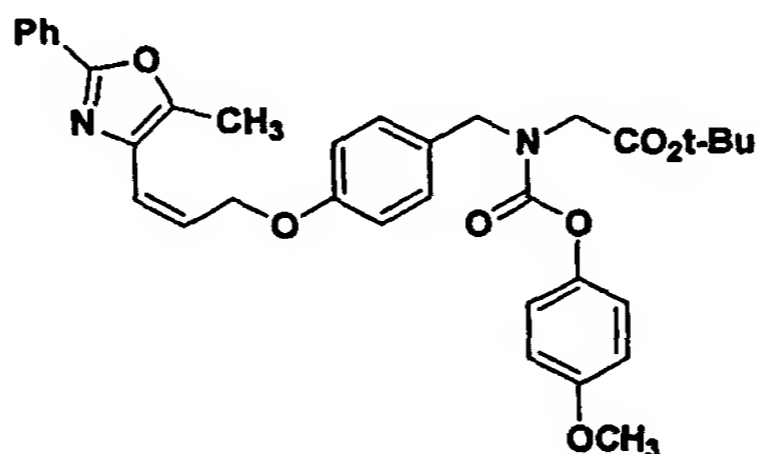
15

Example 545

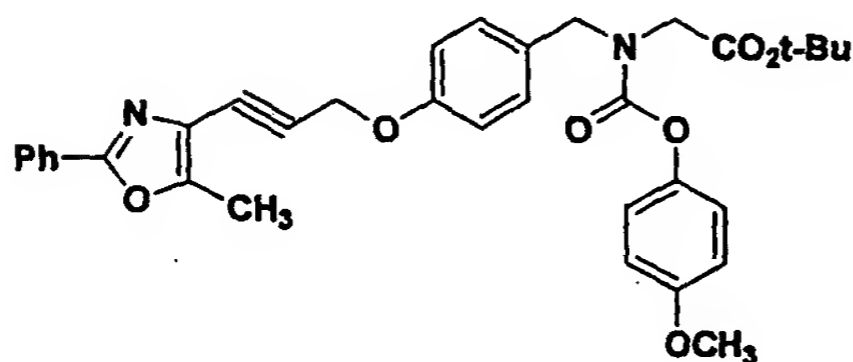


20

A.



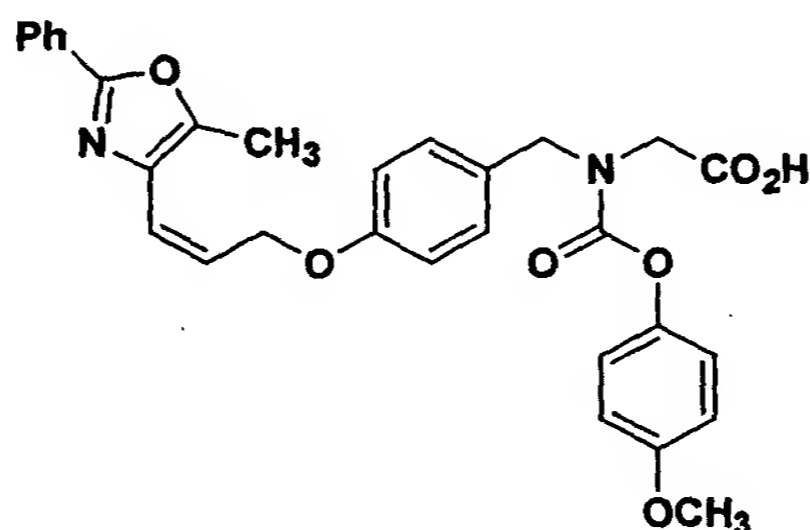
A mixture of the acetylene (38 mg; 0.065 mmol)



(synthesized in a completely analogous fashion to Example 542 Part G compound with glycine tert-butyl ester hydrochloride instead of glycine methyl ester hydrochloride), quinoline (80 mg; 0.62 mmol) and Lindlar's catalyst (8 mg; Pd/CaCO₃; Aldrich) in MeOH (8 mL) was stirred under an atmosphere of H₂ at 0°C for 20 min. Additional Lindlar's catalyst (8 mg; Pd/CaCO₃; Aldrich) was then added and stirring was continued under an atmosphere of H₂ at 0°C for 25 min, after which reaction was complete. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 20 x 100 mm column; flow rate = 20 mL/min; continuous 20 min gradient from 80:20 B:A to 100% B, where A = 90:10:0.1 H₂O:MeOH:TFA and B = 90:10:0.1 MeOH:H₂O:TFA) to give Part A compound (22 mg; 56%) as a colorless oil.

20

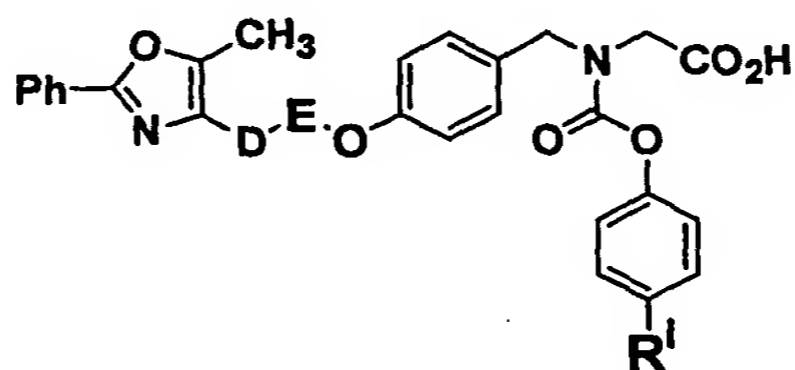
B.

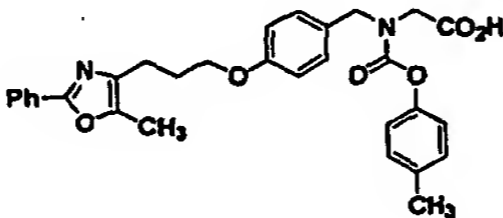
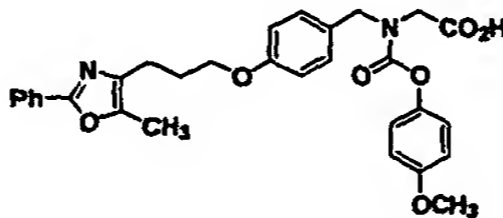
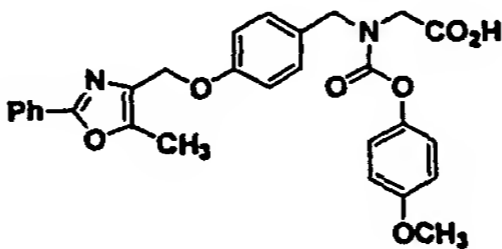
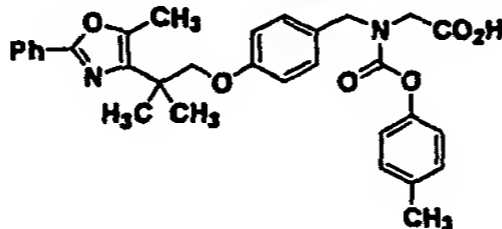
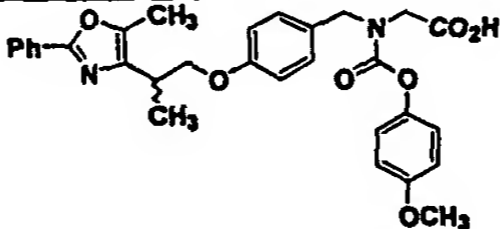


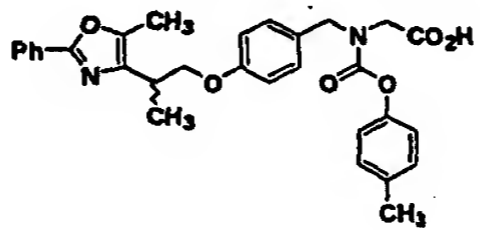
25 To a solution of Part A compound (3 mg; 0.005 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise TFA (0.25 mL) and the reaction was stirred for 2 h at RT. Volatiles were removed in vacuo; the residue was dissolved in CDCl₃,

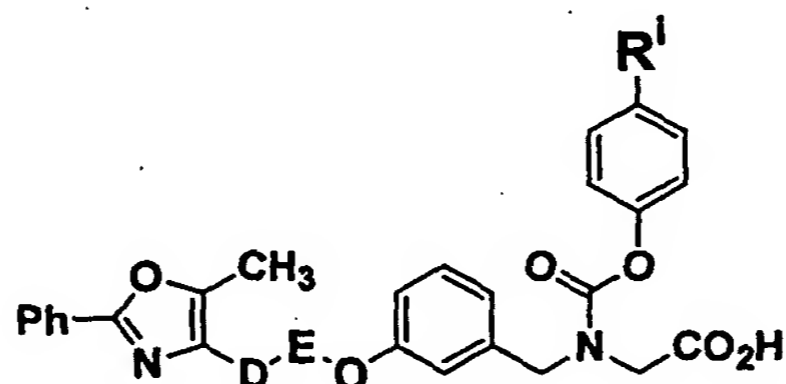
5 Following procedures set out above, Examples 546 to
556 compounds were prepared.

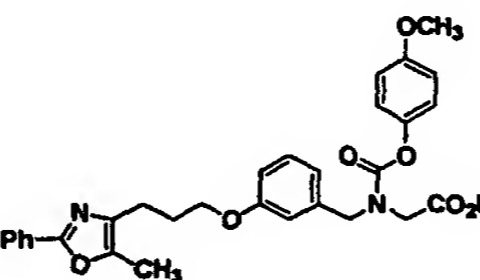
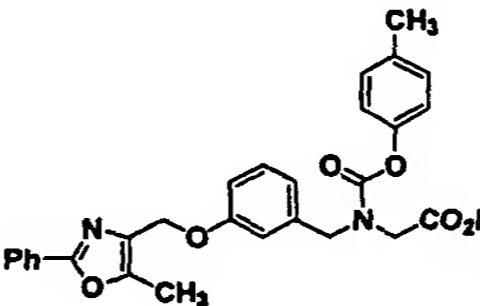
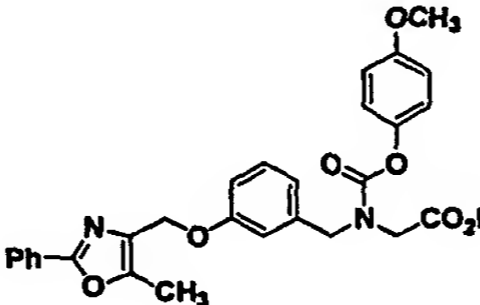
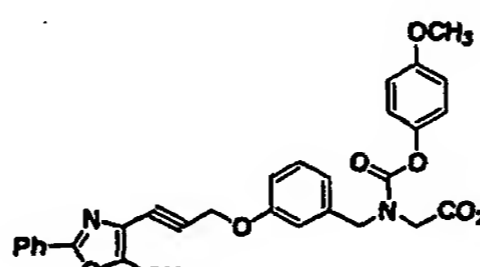
10

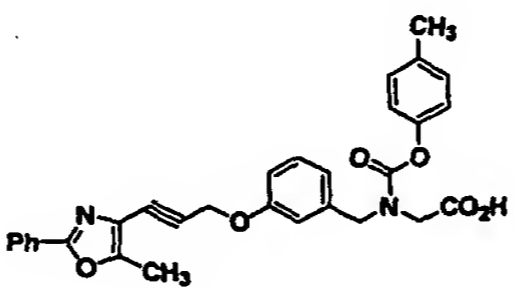


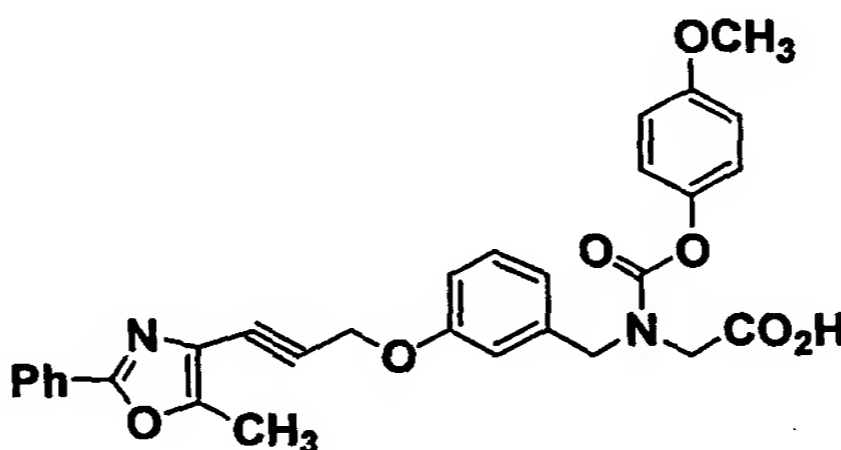
Example No.	Structure	[M+H] ⁺
546		515.4
547		531.3
548		503.3
549		529.4
550		531.2

Example No.	Structure	[M+H] ⁺
551		515.2



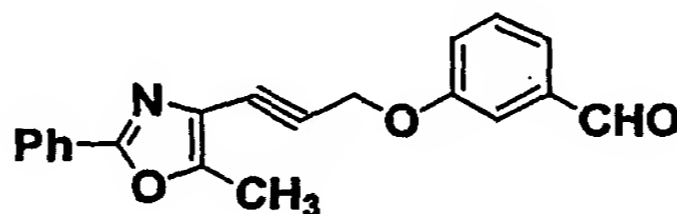
Example No.	Structure	[M+H] ⁺
552		531.3
553		487.3
554		503.3
555		527.2

Example No.	Structure	[M+H] ⁺
556		511.4

Example 555

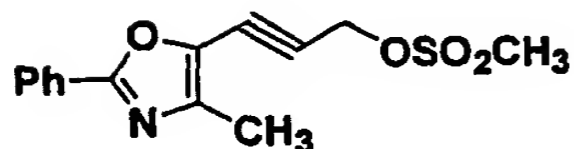
5

A.



10

A mixture of the mesylate (124 mg; 0.43 mmol),



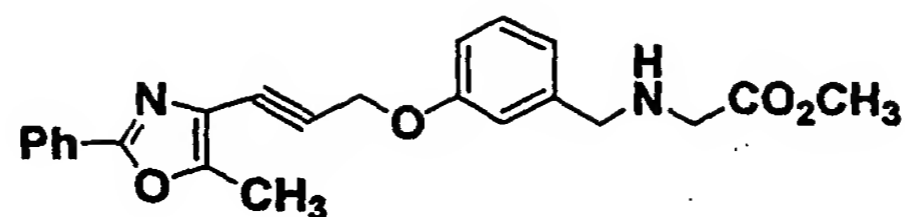
15

3-hydroxybenzaldehyde (62 mg; 0.51 mmol) and K₂CO₃ (94 mg; 0.68 mmol) in CH₃CN (10 mL) were heated at 70°C for 48 h.

20

The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; hex:EtOAc 4:1) to give Part A compound (71 mg; 52%) as a colorless oil. [M + H]⁺ = 318.2

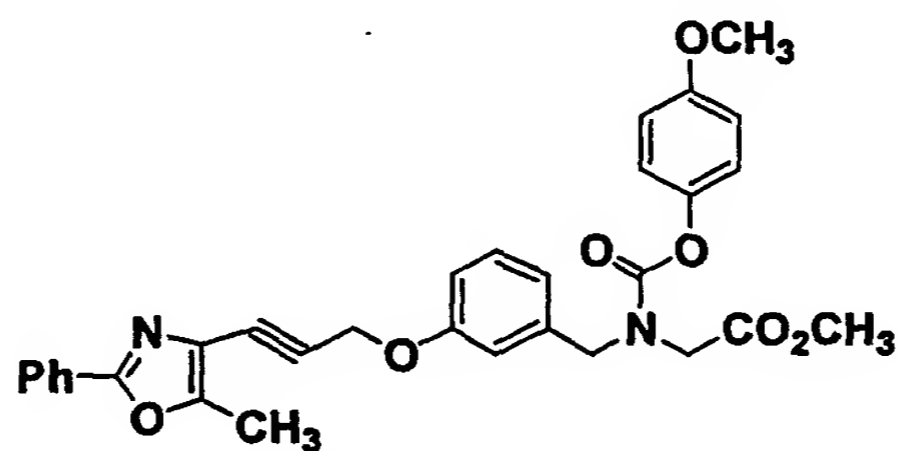
B.



5 To a mixture of Part A compound (71 mg; 0.22 mmol),
glycine.HCl (140 mg; 1.11 mmol) and Et₃N (0.3 mL; 2.16
mmol) in 1,2 dichloroethane (10 mL) was added NaBH(OAc)₃
(150 mg). After stirring at RT for 16 h (reaction
incomplete), more NaBH(OAc)₃ (150 mg) was added. A final
10 addition of NaBH(OAc)₃ (150 mg; in total 2.12 mmol) was
made after another 3 h and the reaction stirred for 48 h
at RT. The reaction was complete at this point;
saturated aqueous NaHCO₃ was added and the aqueous phase
was extracted with CH₂Cl₂ (2x). The combined organic
15 extracts were washed with brine, dried (Na₂SO₄) and
concentrated in vacuo. The residue was chromatographed
(SiO₂; hex:EtOAc = 4:6) to give Part B compound (81 mg;
93%) as a colorless oil.

20

C.

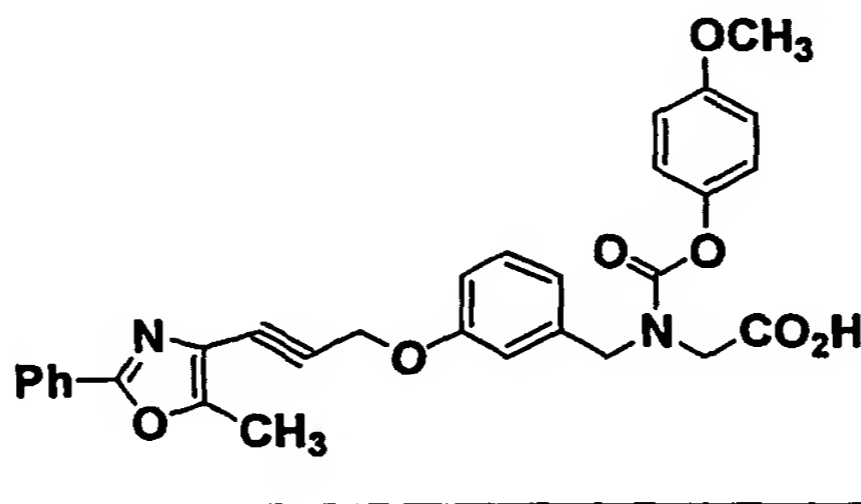


To a solution of Part B compound (10 mg; 0.026
25 mmol) in CH₂Cl₂ (2 mL) were successively added pyridine
(10 μL; 0.12 mmol) and 4-methoxyphenyl chloroformate (10
μL; 0.067 mmol) (each in 0.1 mL CH₂Cl₂). The reaction was
stirred at RT for 16 h, then partitioned between aqueous
1N HCl and EtOAc. The organic phase was washed with
30 brine, dried (Na₂SO₄), and concentrated in vacuo. The
residue was purified by preparative HPLC (YMC S5 ODS 30 x

75 mm column, flow rate = 20 mL/min; continuous gradient from 70:30 A:B to 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA) to give Part C compound (9 mg; 65%).

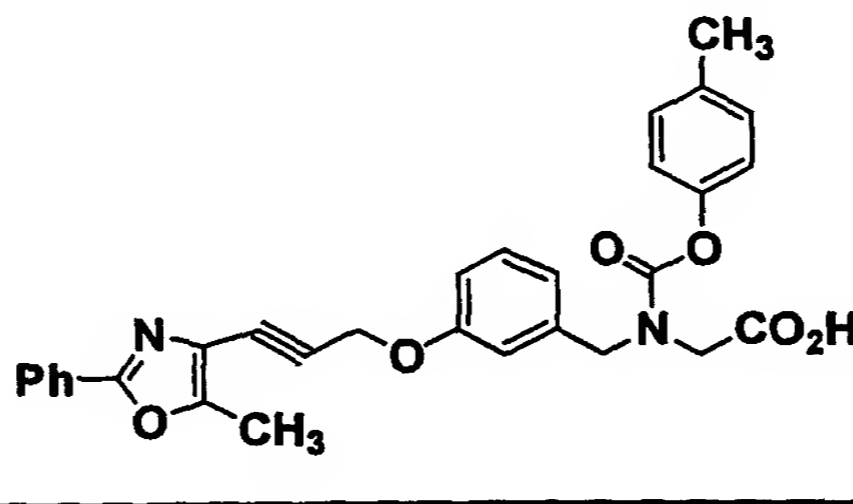
5

D.



10 A solution of Part C compound (9 mg; 0.017 mmol) in 2:1 THF:H₂O (3 mL) was added LiOH (6 mg; 0.14 mmol). The solution was stirred at RT for 4 h, then acidified with excess 1M HCl (aq). The solution was extracted with EtOAc (2 x 5 mL). The combined organic extracts were
15 washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude product was purified by preparative HPLC using the same conditions as above to give title compound (6 mg; 68%) as a colorless film.
[M + H]⁺ = 527.2

20

Example 556

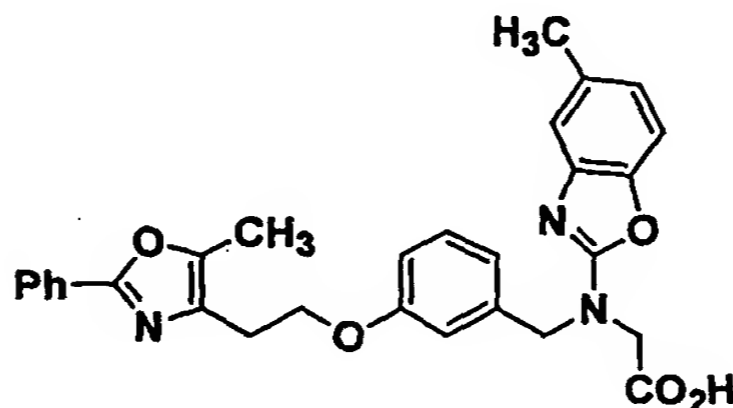
25

Title compound was synthesized using the same sequence as Example 555 compound from Example 555 Part B compound. Acylation with 4-methyl chloroformate (67% after HPLC purification) followed by LiOH hydrolysis

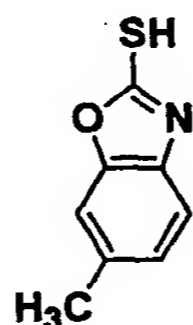
furnished title compound (5 mg; 57% after HPLC purification). $[M + H]^+ = 511.4$

Example 557

5



A.

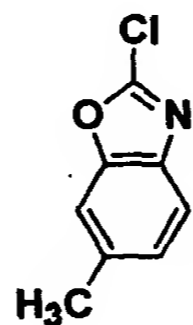


10

A solution of 2-amino-5-cresol (5.0 g; 40 mmol), KOH (3.2 g; 57 mmol) was refluxed in EtOH (50 mL) and CS₂ (40 mL) for 8 h, after which the reaction mixture was concentrated in vacuo. The residue was partitioned between aq 1M HCl (100 mL) and EtOAc (200 mL). The organic phase was washed with water (2 x 100 mL), dried (MgSO₄) and concentrated in vacuo to give Part A compound (4.0 g; 60%) as a white powder.

20

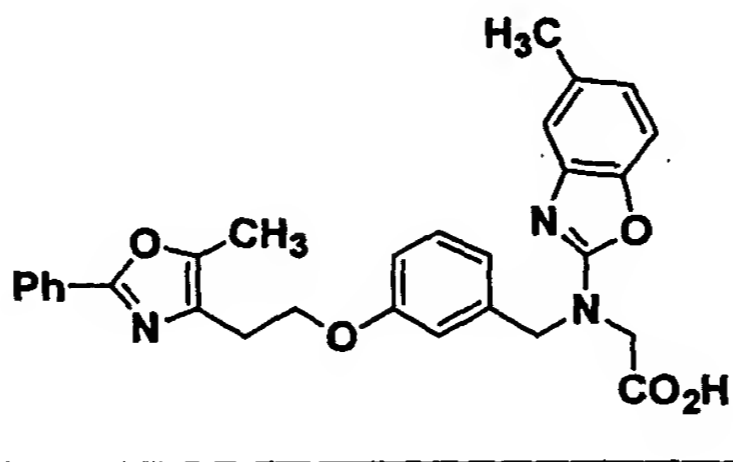
B.



25

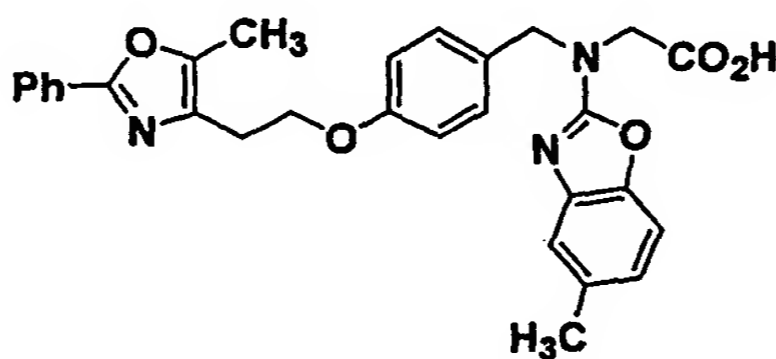
A solution of Part A compound (3.2 g; 19 mmol) and PCl₅ (3.75 g; 19 mmol) in toluene (150 mL) was heated at reflux for 2 h. The reaction mixture was washed successively with water and aqueous NaHCO₃, then dried

5 c.



A solution of the 1,3 benzyl glycine aminoester (150 mg; 0.39 mmol), Part B compound (100 mg; 0.59 mmol) and triethylamine (0.2 mL; 1.98 mmol) in THF (5 mL) was heated at 100°C in a sealed tube for 4 days. At this point LC/MS showed that all starting material had been consumed. Aqueous LiOH (0.5 mL of a 1 M solution) was added and the solution was stirred at RT for 5 h. The mixture was concentrated in vacuo to give an oil, which was purified by preparative HPLC (as for Example 495) to give the title compound (72 mg; 37%) as a solid.

20 Example 558

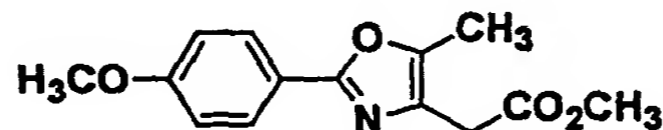


25 A solution of the 1,4 benzyl glycine aminoester (50
mg; 0.13 mmol), Example 557 Part B compound (100 mg; 0.59
mmol) and triethylamine (0.2 mL; 1.98 mmol) in THF (5 mL)
was heated at 100°C in a sealed tube for 4 days. At this
point LC/MS showed that all starting material had been
30 consumed. Aqueous LiOH (0.5 mL of a 1 M solution) was

5

COc1ccc(cc1)-c2nc(CCCOc3ccc(cc3)OCC(=O)NCC(=O)Oc4ccc(cc4)OC)c(C)c2CC(Br)C(=O)CC(=O)OC

B.

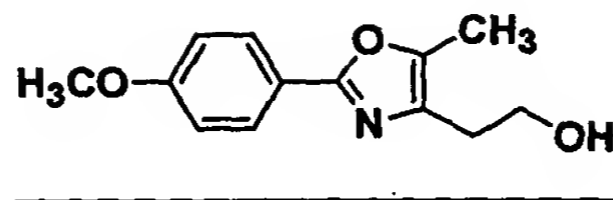


A mixture of Part A compound (1.5 g, 7.2 mmol) and 4-methoxybenzamide (1.0 g, 6.6 mmol) was heated at 100°C for 2.5 h. The reaction mixture was chromatographed

(SiO₂; 5% acetone/CH₂Cl₂) to yield Part B compound (0.57 g, 33%).

C.

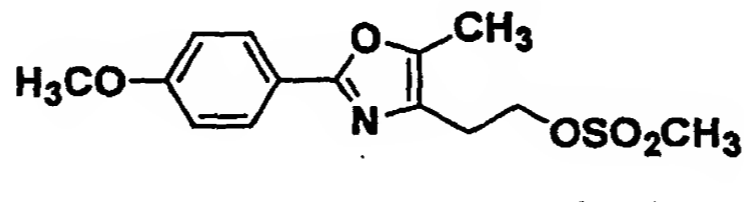
5



To a solution of the ester (0.57 g, 2.3 mmol) in THF (10 mL) was added LiAlH₄ (2.5 mL of a 1 M solution in THF, 2.5 mmol) dropwise over 10 min and the reaction was stirred at RT for 0.5 h. The reaction was quenched by adding a few drops of water and then partitioned between EtOAc (50 mL) and brine (10 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo to give Part C (0.52 g, >95%) as an oil which was used in the following reaction without further purification.

D.

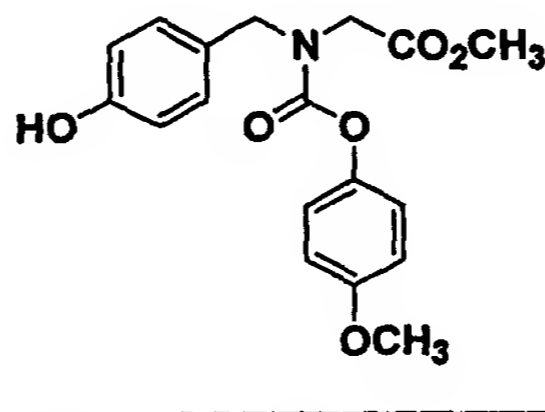
20



A mixture of Part C compound (0.52 g, 2.3 mmol), CH₃SO₂Cl (0.25 mL, 3.3 mmol) and Et₃N (0.5 mL, 3.6 mmol) in CH₂Cl₂ (10 mL) was stirred at RT for 12 h. Volatiles were removed in vacuo, and the residue was chromatographed (SiO₂; 4% acetone/CH₂Cl₂) to provide Part D compound (0.61 g, 85% for 2 steps) as a colorless oil.

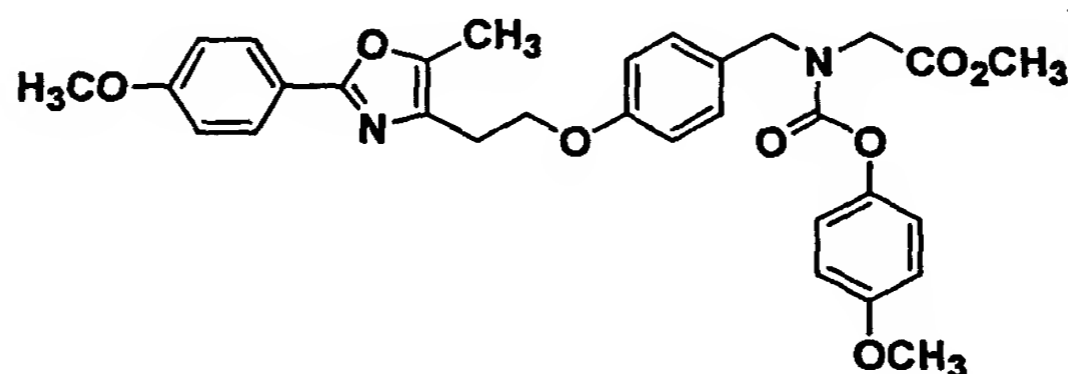
E.

30



To a mixture of crude Example 541 Part C compound (synthesized using 4-hydroxybenzaldehyde [2.0 g; 16 mmol] and glycine methyl ester hydrochloride [2.3 g; 18 mmol]) in dioxane:H₂O (100 mL of a 1:1 mixture) were successively
5 added NaHCO₃ (2.5 g; 30 mmol; in one portion) and 4-methoxyphenyl chloroformate (2.0 mL; 14 mmol) dropwise. The reaction was stirred at RT for 12 h and then extracted with EtOAc (4 x 150 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo.
10 The residue was chromatographed (SiO₂; 3% acetone/CH₂Cl₂) to provide Part E compound (2.4 g; 44%) as a colorless oil.

F.

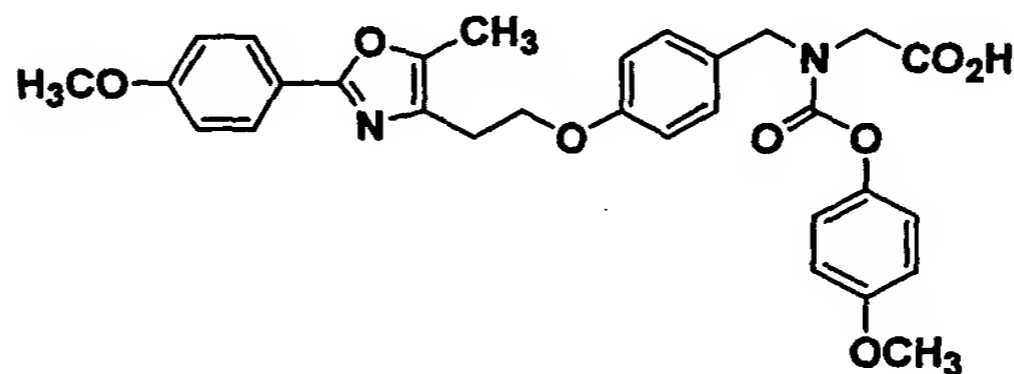


15

A mixture of Part E compound (86 mg, 0.25 mmol), Part D compound (60 mg, 0.20 mmol) and K₂CO₃ (50 mg, 3.7
20 mmol) in DMF (3 mL) was heated at 80°C for 12 h. The reaction was cooled to RT and filtered. Volatiles were removed in vacuo and the residue was chromatographed (SiO₂; 7:3 hexane:EtOAc) to provide title compound (41 mg; 36%) as a colorless oil.

25

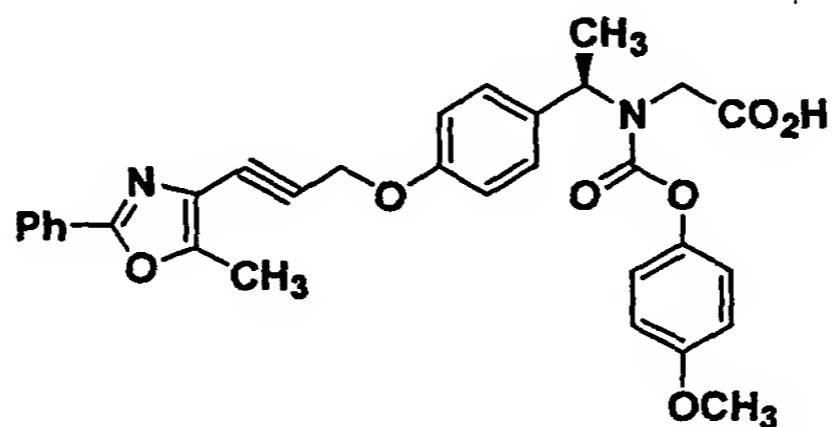
G.



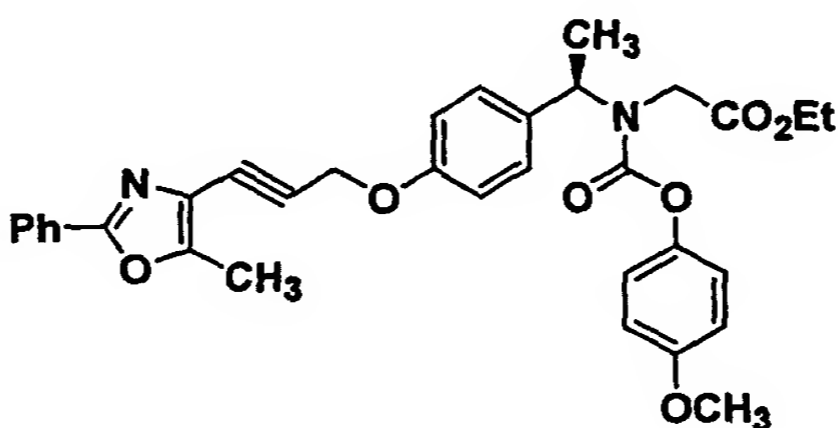
A solution of Part F compound (41 mg, 0.071 mmol) and LiOH.H₂O (34 mg; 0.8 mmol) in THF-H₂O (2 mL of a 2:1 mixture) was stirred at RT for 2 h. The reaction mixture was acidified to pH ~ 2 with 1 M aqueous HCl, then was
5 extracted with EtOAc. The combined organic extracts were concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; 30 min continuous gradient from 50% A:50% B to 100% B, where solvent A = 90:10:0.1
10 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA) to provide title compound (17 mg, 40%) as a colorless oil. [M + H]⁺ = 547.23

Example 560

15

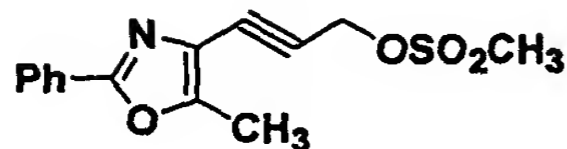


A.

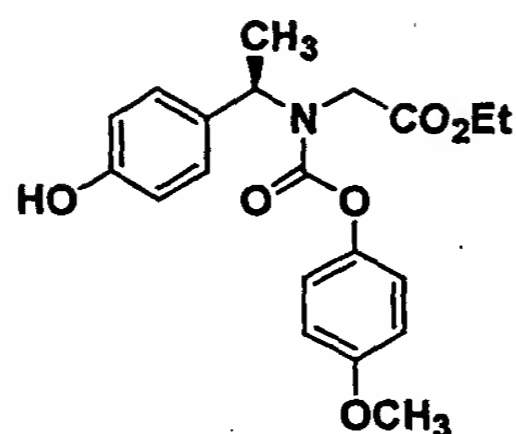


20

A mixture of the mesylate (18 mg; 0.061 mmol)



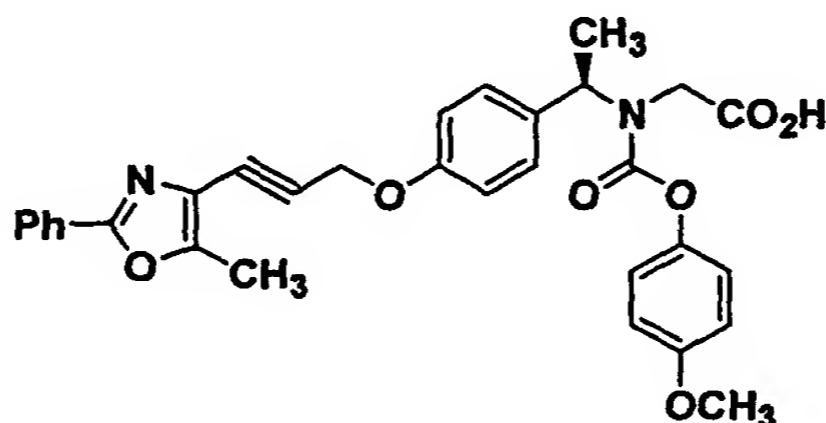
25 the ester,



[described in the synthesis of Example 503 Part B compound (50 mg; 0.13 mmol)], K_2CO_3 (17 mg; 0.34 mmol) in CH_3CN (1 mL) were heated at 70°C for 24 h. Additional
 5 K_2CO_3 (30 mg) and CH_3CN (1 mL) were added and the mixture was heated at 75°C for another 48 h. The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the crude
 10 product. This was purified by preparative HPLC (YMC S5 ODS 50 x 75 mm column; continuous gradient from 70:30 B:A to 100% B, where A = 90:10:0.1 H_2O :MeOH:TFA and B = 90:10:0.1 MeOH: H_2O :TFA) to give Part A compound (13 mg; 35%) as a colorless oil.

15

B.

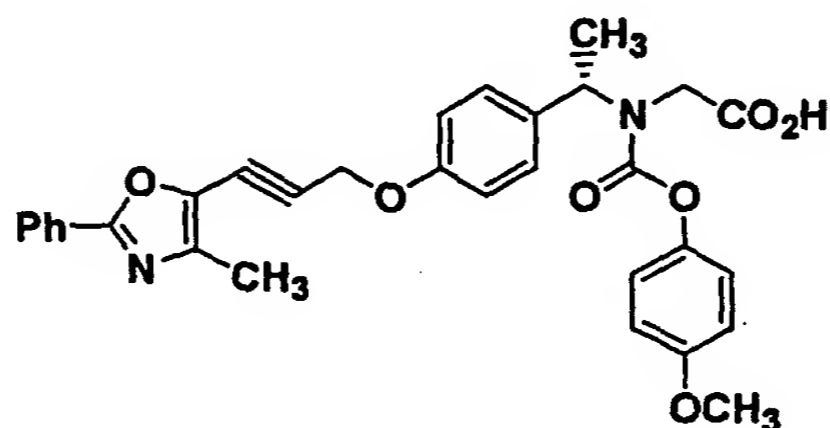


20 To a solution of Part A compound (12 mg; 0.021 mmol) in 2:1 THF: H_2O (1.5 mL) was added LiOH (8 mg; 0.19 mmol). The solution was stirred at RT for 24 h, then acidified with excess 1M HCl (aq). The solution was extracted with EtOAc (2 x 5 mL). The combined organic
 25 extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by

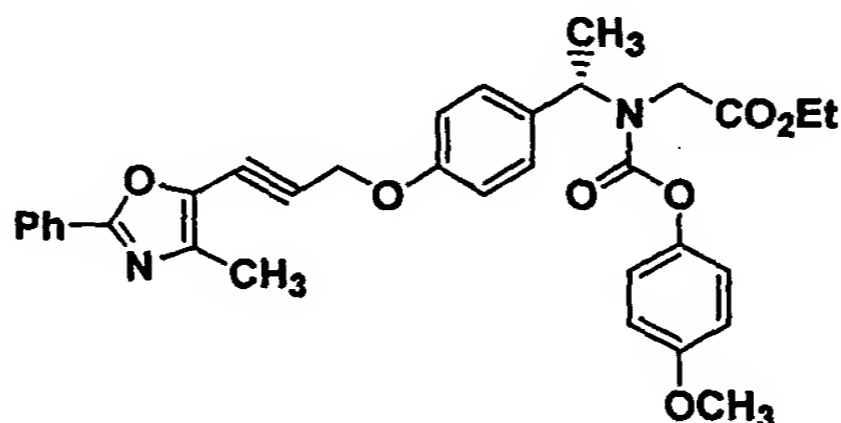
preparative HPLC using the same conditions as above to give title compound (6.4 mg) as a colorless film.

$$[M + H]^+ = 541.3$$

5

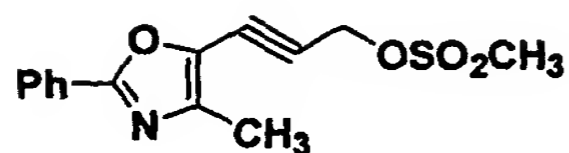
Example 561

A.



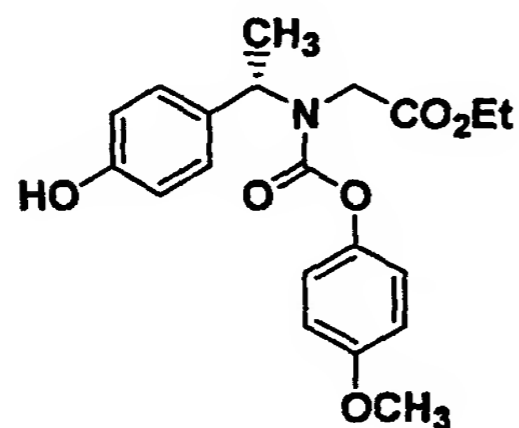
10

A mixture of the mesylate (18 mg; 0.061 mmol)



15

the phenol (50 mg; 0.13 mmol)

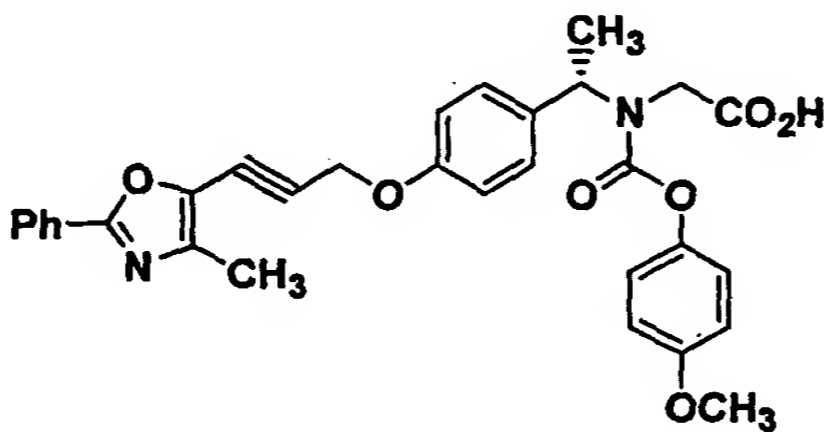


20

K_2CO_3 (17 mg; 0.34 mmol) in CH_3CN (1 mL) were heated at $70^\circ C$ for 24 h. Additional K_2CO_3 (30 mg) and CH_3CN (1 mL) were added and the mixture was heated at $75^\circ C$ for another 48 h. The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine.

The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by preparative HPLC (YMC 55 ODS 50 x 75 mm column; continuous gradient from 70:30 B:A to 100% B, where A = 90:10:0.1 H_2O :MeOH:TFA and B = 90:10:0.1 MeOH: H_2O :TFA) to give Part A compound (13 mg; 35%) as a colorless oil.

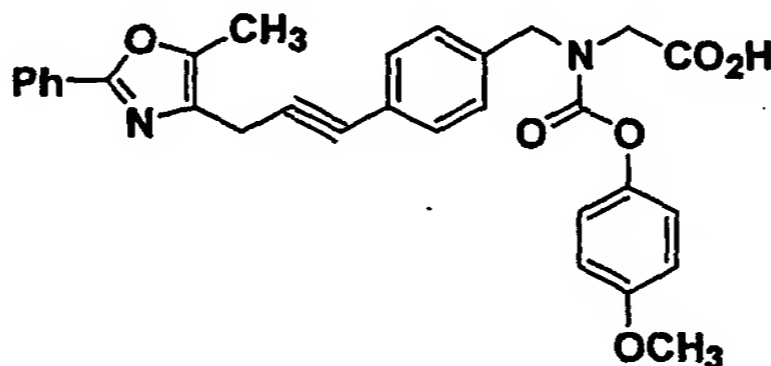
B.



10

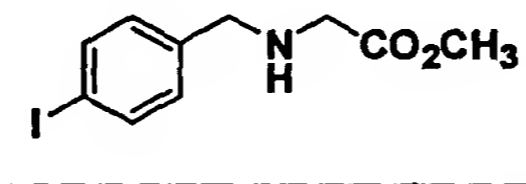
To a solution of Part A compound (12 mg; 0.021 mmol) in 2:1 THF: H_2O (1.5 mL) was added LiOH (8 mg; 0.19 mmol). The solution was stirred at RT for 24 h, then acidified with excess 1M HCl (aq). The solution was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by preparative HPLC using the same conditions as above to give title compound. $[\text{M} + \text{H}]^+ = 541.3$

20

Example 562

25

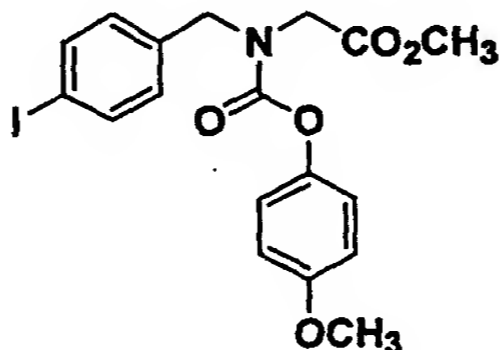
A.



A solution of 4-iodobenzaldehyde (1.0 g; 4.31 mmol) and glycine methyl ester hydrochloride (0.65 g; 5.17 mmol) and Et₃N (0.50 g; 4.95 mmol) in MeOH (15 mL) was stirred at RT for 4 h. The mixture was cooled to 0°C and
5 a solution of NaBH₄ (230 mg; 6.0 mmol) in MeOH was added portionwise. The mixture was allowed to warm to RT and stirred overnight at RT. Volatiles were removed in vacuo (without heating) and the residue was partitioned between aq NaHCO₃ and EtOAc. The aqueous phase was extracted with
10 EtOAc (3x). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give Part A compound as an oil. This material was used in the next step without further purification.

15

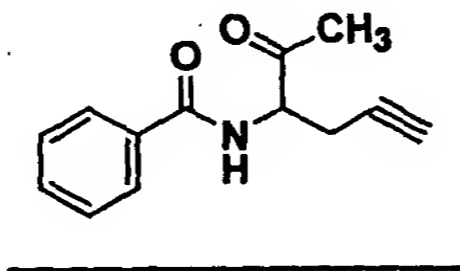
B.



To a solution of the crude Part A compound and Et₃N
20 (0.80 g; 8.00 mmol) in CH₂Cl₂, was added a solution of 4-methoxyphenyl chloroformate (0.93 g; 5.00 mmol) in CH₂Cl₂. The reaction mixture was stirred at RT overnight, then partitioned between saturated aq NaHCO₃ and EtOAc. The aqueous phase was extracted with EtOAc (2x); the combined
25 organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give a residue, which was chromatographed (SiO₂; hex:EtOAc 3:1) to give Part B compound (1.2 g; 61%) as an oil.

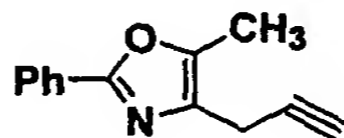
30

C.



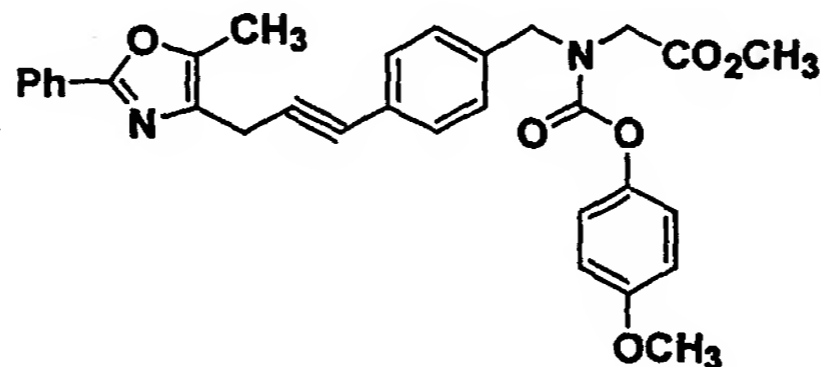
To a 0°C solution of DL-propargyl glycine (3.0 g; 26.5 mmol) in pyridine (20 mL; 247 mmol) was added dropwise benzoyl chloride (3.73 g; 26.5 mmol). The solution was allowed to warm to RT and stirred at RT for 1 h. Acetic anhydride (10 mL) was added and the mixture was stirred at 90°C for 2 h. The reaction mixture was diluted with H₂O (35 mL) and extracted with EtOAc (3x); the combined organic extracts were washed with aqueous 1N HCl, H₂O, aqueous NaHCO₃, and finally water. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (SiO₂; stepwise gradient from 5:1 to 3:1 hex:EtOAc) to give Part C compound (1.0 g; 17%) as an orange solid.

15 D.



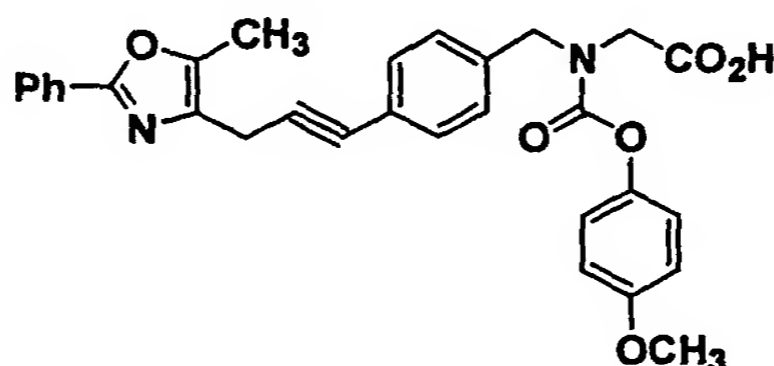
A solution of Part C compound (1.0 g; 4.65 mmol), trifluoroacetic anhydride (3 mL) and TFA (3 mL) in a sealed tube was heated at 40°C for 8 h. Volatiles were removed in vacuo and the residue was dissolved in EtOAc (50 mL). The solution was washed repeatedly with saturated aq NaHCO₃ (until all acid had been removed from the organic phase), then brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; 6:1 hex:EtOAc) to give Part D compound (800 mg; 87%; >98% pure by HPLC) as an oil.

30 E.



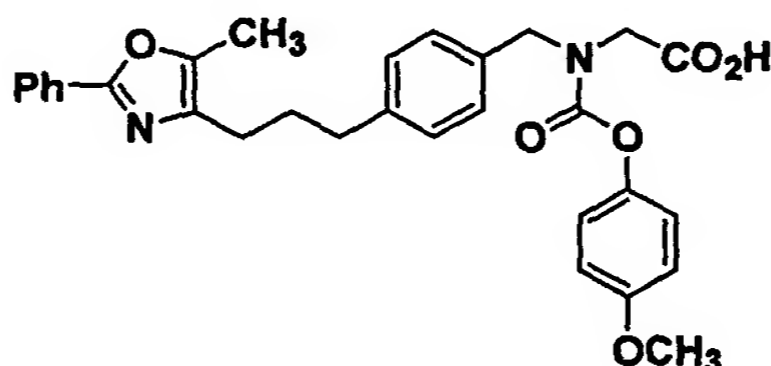
A mixture of Part D compound (100 mg; 0.507 mmol), Part B compound (254 mg; 0.558 mmol), CuI (2 mg; 0.01 mmol) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (4 mg; 0.005 mmol) in diethylamine (2 mL) was stirred at RT for 3h under N_2 . At this point
5 HPLC/MS showed that all starting material had been consumed and the presence of a peak which corresponded to the desired product. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO_2 ; stepwise gradient from 5:1 to
10 2:1 hex:EtOAc) to provide Part E compound (200 mg; 75%) as an oil.

F.



15

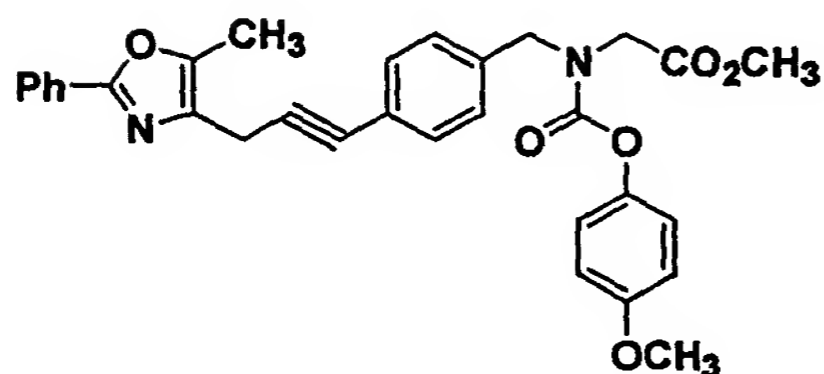
A solution of Part E compound (20 mg; 0.038 mol) in HOAc/conc HCl (1 mL of a 10:1 solution) was stirred at 45°C overnight. Volatiles were removed in vacuo and the
20 residue was purified by preparative HPLC (YMC S5 ODS reverse phase column; 30 x 250 mm; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where solvent A = 90:10:0.1 H_2O :MeOH:TFA and solvent B = 90:10:0.1 MeOH: H_2O :TFA) to give the title compound (6.8
25 mg; 35%) as a lyophilate. $[\text{M} + \text{H}]^+ = 511.2$

Example 563

30

COC(=O)CN(Cc1ccc(cc1)CCCCc2c(C)c(Oc3ccccc3)n2)C(=O)Oc4ccc(OC)cc4

A solution of Example 562 Part E compound



(38 mg; 0.072 mmol) in MeOH (5 mL) was stirred under an atmosphere of H₂ in the presence of 10% Pd/C catalyst (10 mg) at RT for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give Part A compound (35 mg; 92%) as an oil.

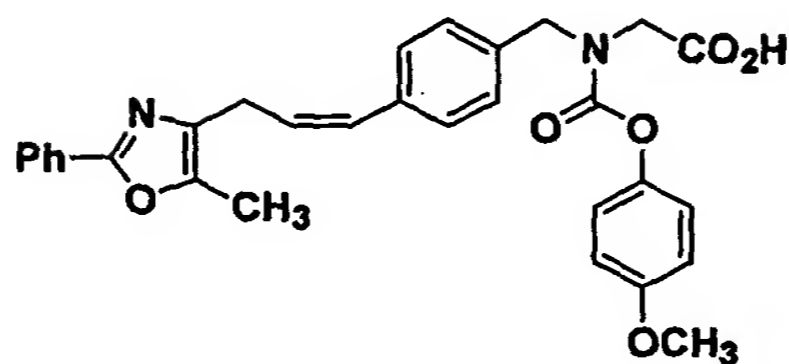
CC1=C(C(=N1C2=CC=CC=C2)CCCCC3=CC=CC=C3)C(=O)N(CCC(=O)O)C(=O)Oc4ccc(OC)cc4

A solution of Part A compound (35 mg; 0.066 mmol) in aqueous LiOH (1 mL of a 1M solution) and THF (5 mL) was stirred at RT for 2h. The reaction was acidified to pH 3 with excess aqueous 1M HCl and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS reverse phase column; 30 x 250 mm; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where solvent A = 90:10:0.1 H_2O :MeOH:TFA and solvent B =

5

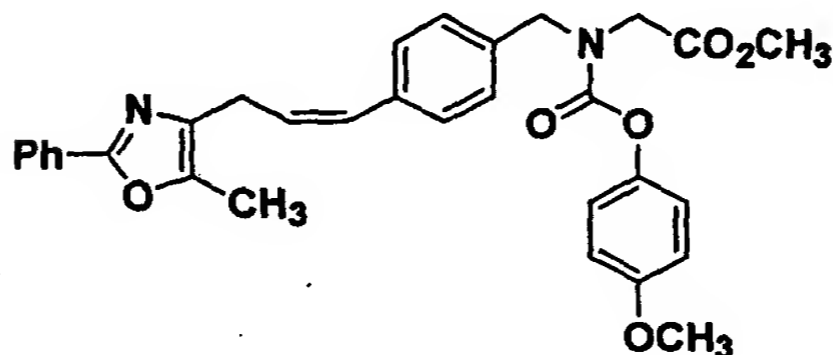
CC1=C(C(=C(C=C1)C=CC=CC2=CC=CC=C2)C(=O)NCC(=O)OC3=CC=C(OC)C=C3)C=C(C=C1)C4=CC=CC=C4N=C5C(=C(C=C5)C)OCOC(=O)CN(Cc1ccc(cc1)/C=C/C2=C(C)C(=N2)c3ccccc3)C(=O)Oc4ccc(OC)cc4

15
20

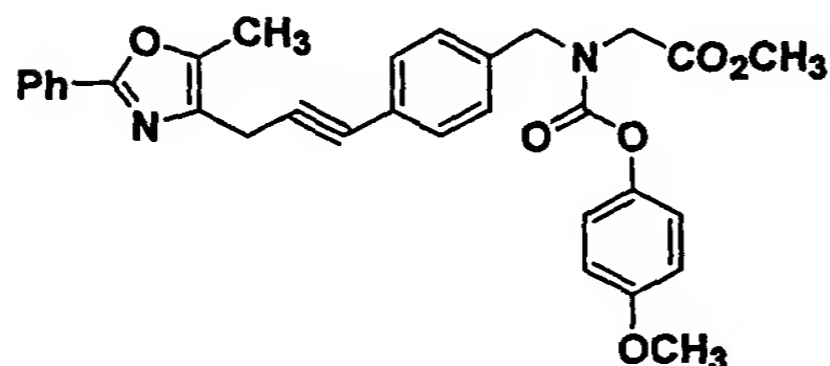
Example 565

5

A.

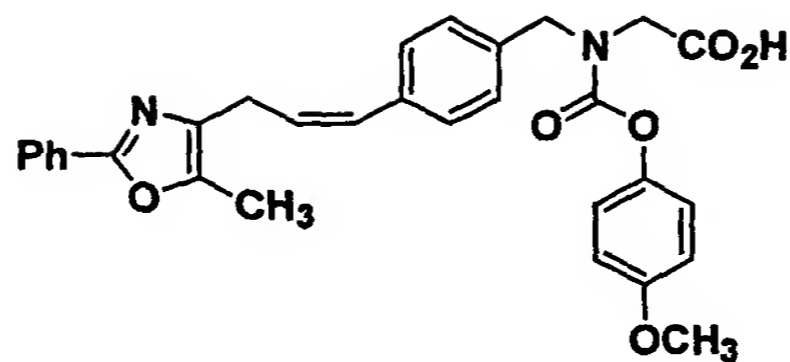


A mixture of Example 562 Part E compound

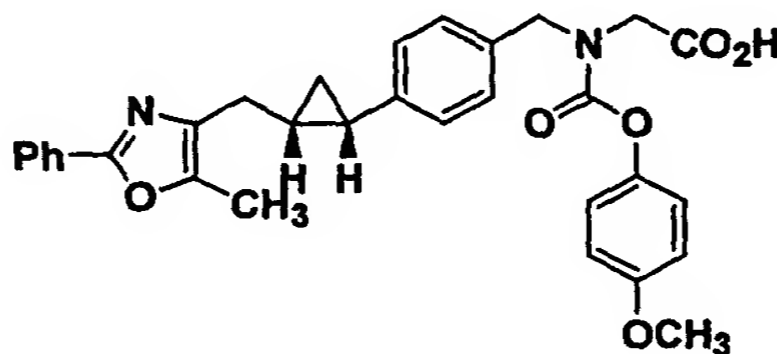


- 10 (80 mg; 0.15 mmol), quinoline (2 μ L; 0.01 mmol) and Lindlar's catalyst (7 mg; 5% Pd/CaCO₃) in toluene (2 mL) was stirred under an atmosphere of H₂ for 2 h. More Lindlar's catalyst (20 mg) was then added and stirring was continued under H₂ for another 2 h, after which the
- 15 reaction was complete by analytical HPLC. The reaction mixture was filtered (Celite®) and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from 3:1 to 2:1 hexane:EtOAc) to give Part A compound.

B.

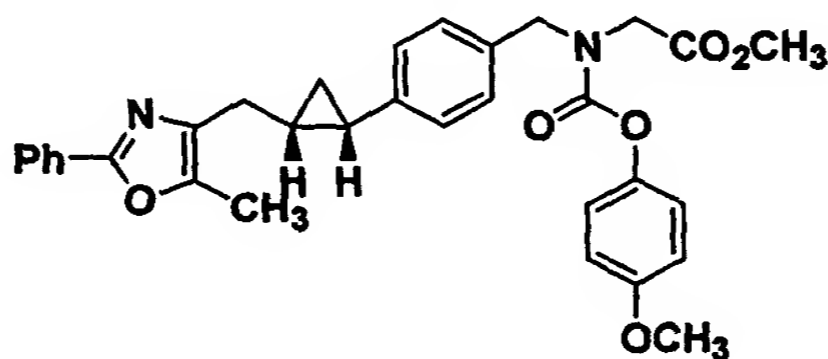


A solution of Part A compound and aqueous LiOH (1 mL of a 1 M solution; 1 mmol) in THF was stirred at RT overnight. The reaction mixture was acidified with excess aqueous 1 M HCl and extracted with EtOAc (2x). The combined organic extracts were concentrated in vacuo. The residue was purified by preparative HPLC (as for Example 495) to give the title compound (14 mg; 18%) as a white solid. $[M + H]^+ = 513.3$

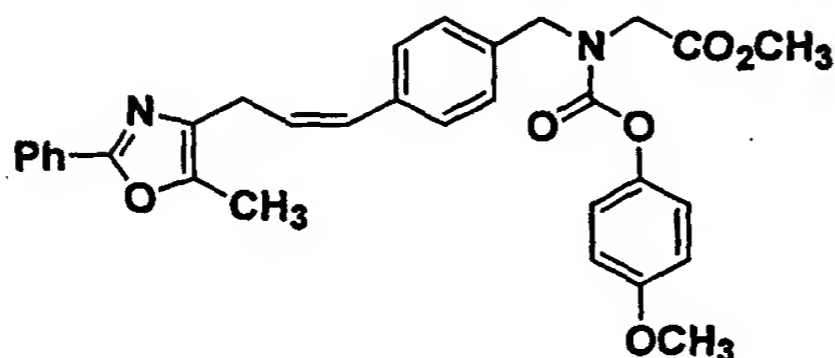
Example 566 (racemic)

15

A.



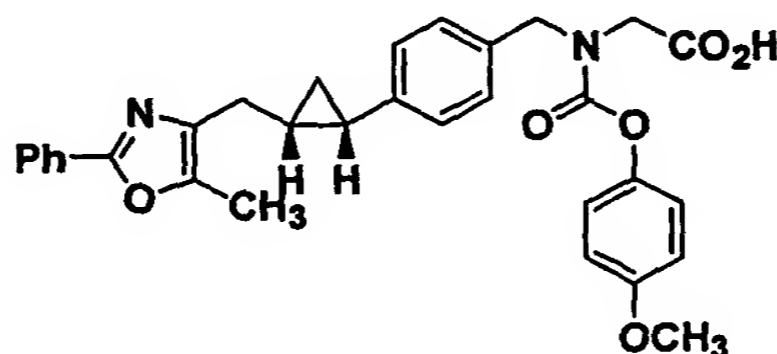
To a 0°C solution of Example 565 Part A compound



(60 mg; 0.11 mmol) in DCE (3 mL) was added dropwise diethylzinc (43 μ L; 0.29 mmol). The solution was stirred at 0°C for 10 min and iodochloromethane (244 μ L; 0.57 mmol) was then added. The reaction was allowed to warm to RT and stirred at RT for 3 h, then was cautiously quenched by addition of aqueous HCl (1 mL of a 1 M solution). The aqueous layer was extracted with EtOAc (2x); the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; stepwise gradient from 3:1 to 2:1 hexane:EtOAc) to give crude Part A compound, which was used in the next step without further purification.

15

B.



A solution of crude Part A compound and aqueous
20 LiOH (1 mL of a 1 M solution; 1 mmol) in THF was stirred
at RT overnight. The reaction mixture was acidified with
excess aqueous 1 M HCl and extracted with EtOAc. The
combined organic extracts were concentrated in vacuo.
The residue was purified by preparative HPLC (conditions)
25 to give the title compound (7 mg; 12% over 2 steps) as a
white solid. $[M + H]^+ = 527.2$.

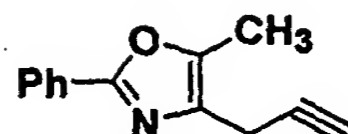
Example 567



A.

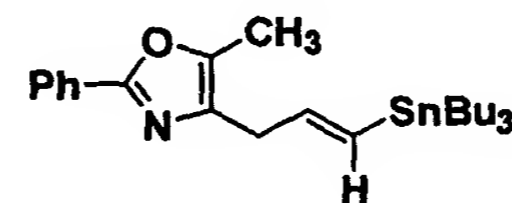


10



15

B.



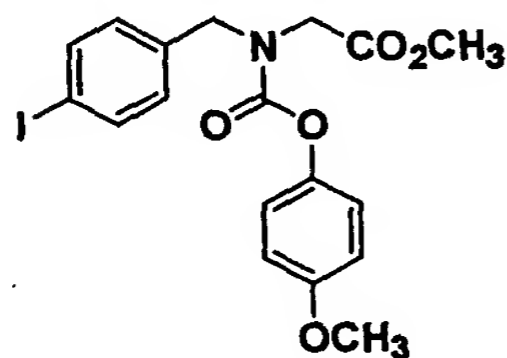
20

25

5

COC(=O)CN(Cc1ccc(cc1)/C=C/Cc2c(C)c(Oc3ccccc3)n2)c(=O)Oc4ccc(OC)cc4

A solution of Part B compound (100 mg; 0.020 mmol) and Example 562 Part B compound



20

CC1=C(C=C(C=C1C2=CC=CC=C2N=C3C(=C(C=C3)C)C(=O)OCC(=O)Oc4ccc(OC)cc4)C=C/C=C/c5ccc(cc5)C6=CC=CC=C6)C

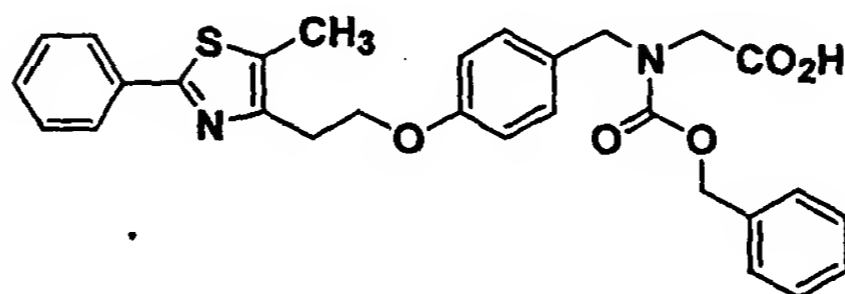
25

5

Examples 568 to 572

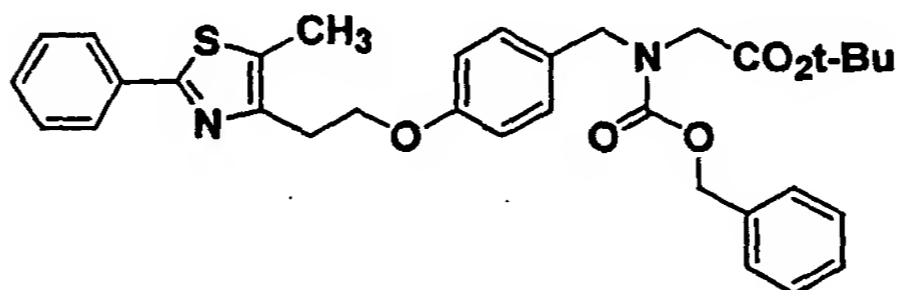
15

Example No.	Structure	[M+H] ⁺
568		511.2
569		515.9
570		511.2
571		513.2
572		513.3

Example 573

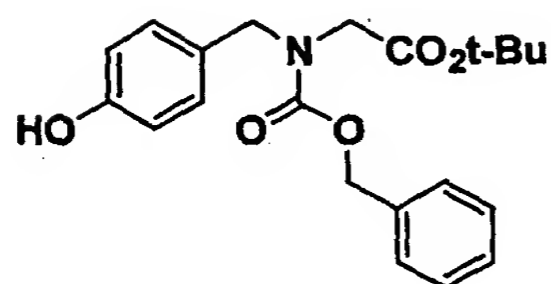
5

A.



10

To a mixture of the amino-ester (27 mg; 0.073 mmol)

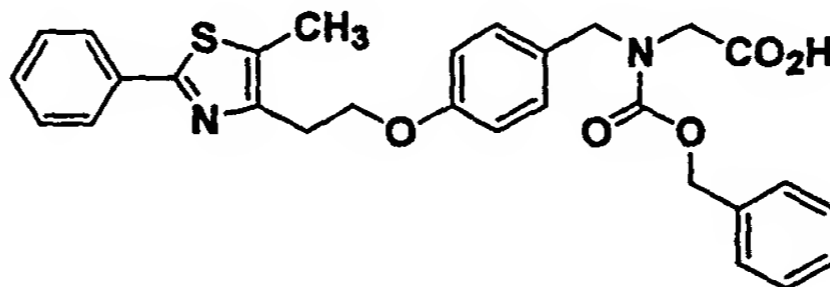


15

5-methyl-2-phenyl-thiazol-4-yl-ethanol (25 mg; 0.11 mmol; Maybridge) resin-bound Ph_3P (27 mg; 0.081 mmol) in CH_2Cl_2 (0.5 mL) was added DEAD (20 μL ; 0.13 mmol). The reaction was stirred at RT for 6 h, then was filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 100 mm column; flow rate = 50 mL/min; continuous gradient from 30:70 B:A to 100% B, where solvent A = 90:10:0.1 $\text{H}_2\text{O}:\text{MeOH}:\text{TFA}$ and solvent B = 90:10:0.1 $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$) to furnish Part A compound.

20

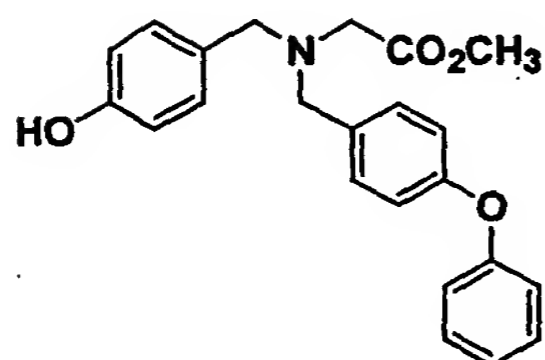
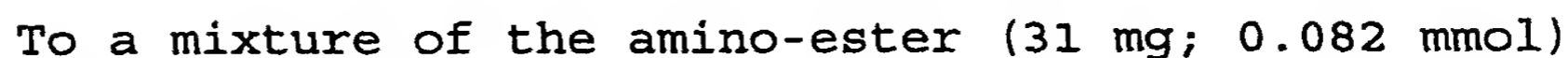
B.



25

5

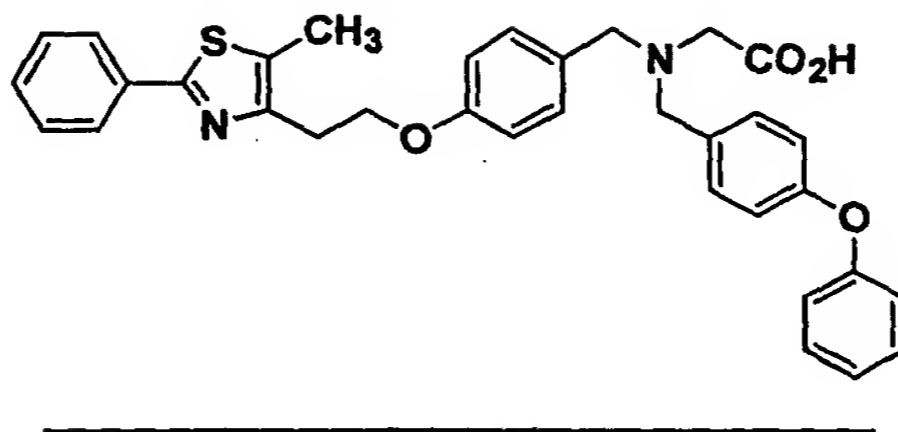
10



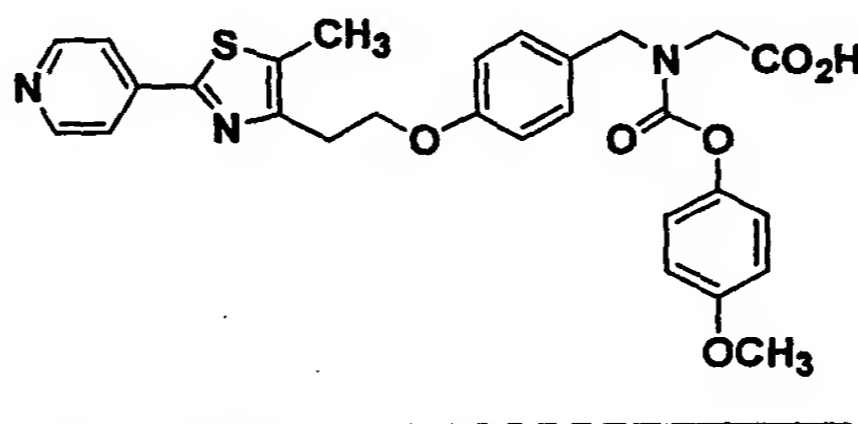
15

20

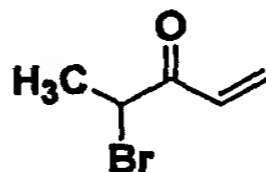
B.



5 A solution of crude Part A compound and LiOH.H₂O (20 mg; 0.48 mmol) in THF:MeOH:H₂O (1 mL of a 3:1:1 mixture) was stirred at RT overnight. The reaction was acidified to pH ~4 with aqueous 1N HCl, then was extracted with EtOAc (2x). The combined organic extracts
 10 were concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 100 mm column; flow rate = 50 mL/min; 10 min continuous gradient from 30:70 B:A to 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA) to furnish title
 15 compound (16 mg; 34%) as a brown oil (95% purity by analytical HPLC). [M + H]⁺ = 565.2

Example 575

A.

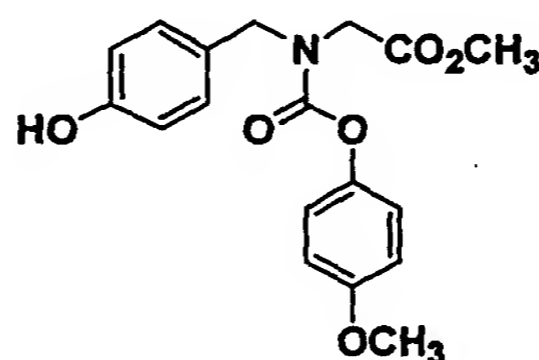


25 To a solution of 2,4-dibromo-3-pentanone (Avocado Chemicals, 19.6 g, 80 mmol) in CH₂Cl₂ (50 mL) was added dropwise Et₃N (30 mL, 210 mmol) over 30 min; the resulting solution was heated to reflux for 12 h. The reaction mixture was cooled to RT, then was poured into ice and

5

CC(C)C(=O)CCOC1=CC=C(C=C1)CN(C)C(=O)Oc2ccc(OC)cc2COC(=O)C

A mixture of Example 559 Part E compound (0.60 g, 1.7 mmol),



15

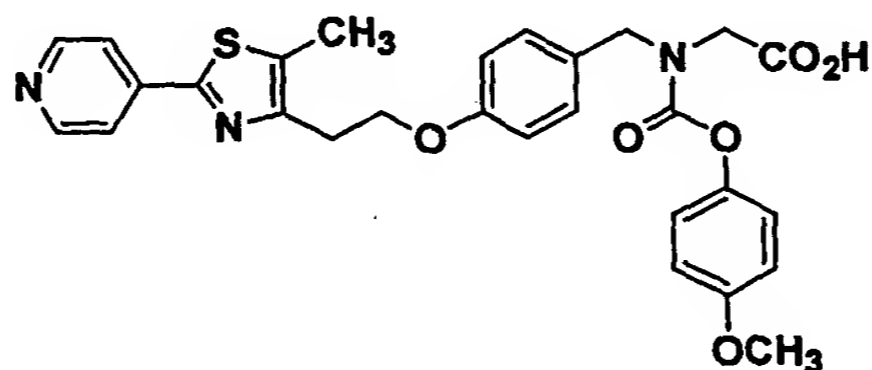
CCOC(=O)CN(Cc1ccc(OCCc2c(C)c(s2)C3=CC=CC=N3)cc1)C(=O)Oc4ccc(OC)cc4

25

A solution of Part B compound (40 mg, 0.080 mmol) and thioisonicotinamide (50 mg, 0.36 mmol) in toluene-EtOH (3 mL of a 1:1 mixture) was heated at 55°C for 12 h. The reaction was cooled to RT and volatiles were removed in vacuo. The crude product was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm, continuous 30 min gradient from 30% B:70% A to 100% B at 30 min, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA) to give Part C compound (17; 39%) as an oil.

10

D.



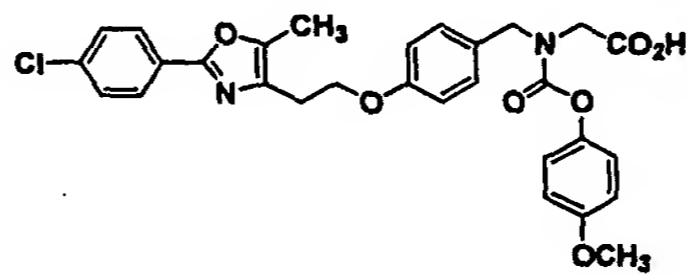
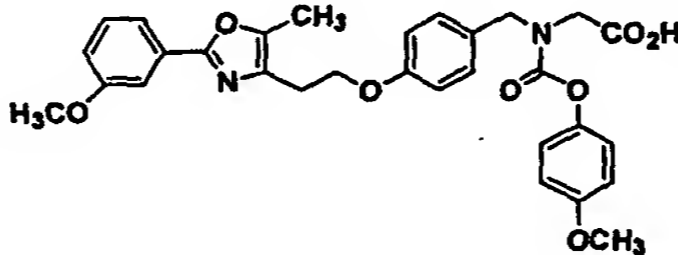
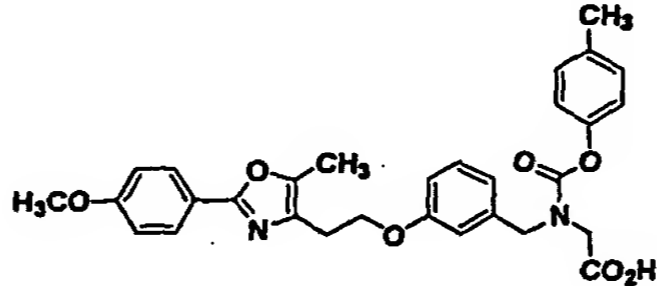
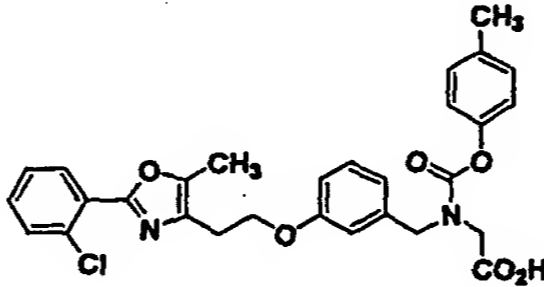
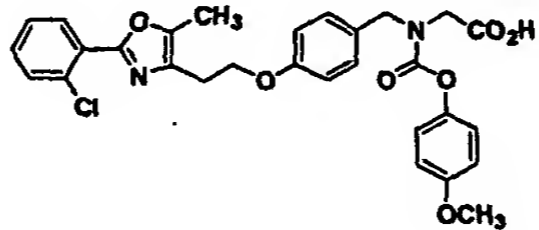
15 A solution of Part C compound (17 mg, 0.031 mmol) and LiOH.H₂O (40 mg, 1 mmol) in THF-H₂O (3 mL of a 2:1 mixture) was stirred at RT for 2 h. The reaction mixture was acidified by addition of acetic acid and then partitioned between H₂O (2 mL) and EtOAc (5 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo to provide the title compound (13.7 mg, 81%) as a white solid. [M + H]⁺ = 534.2

20

Examples 576 to 580

Following the procedures set out hereinbefore and in the working Examples, the following compounds were prepared.

5

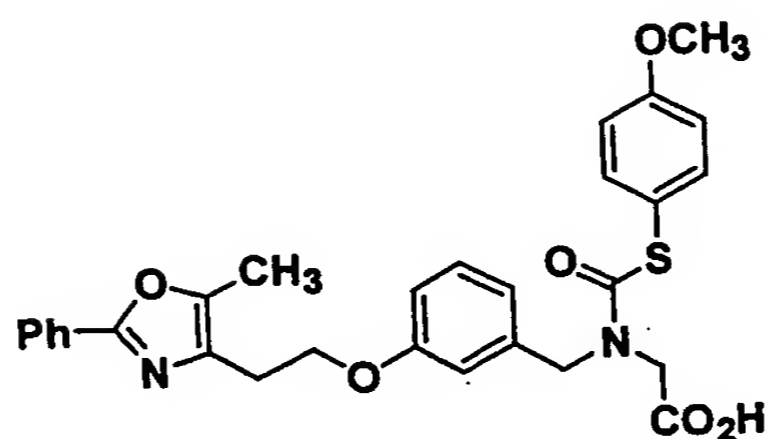
Example No.	Structure	[M+H] ⁺
576		551.2; 553.2
577		547.2
578		531.2
579		535.2; 537.2
580		551.2; 553.2

5

10

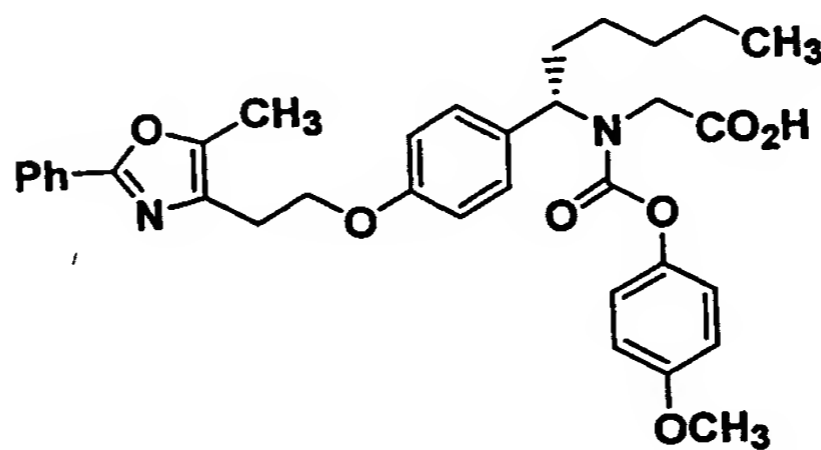
10

Example	Structure	[M+H] ⁺
583		533.3
584		533.3

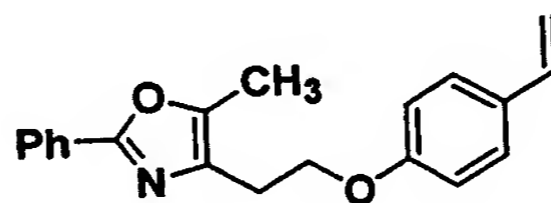
Example 584

5 ^1H NMR (CDCl_3 ; 400 MHz): δ 2.42 (s, 3H), 3.04 (br s; 2H), 3.79 (s, 3H), 4.03 (br s, 2H), 4.25 (br s, 2H), 4.70 (br s, 2H), 6.8-7.0 (m, 5H), 7.15-7.30 (m, 1H), 7.35-7.50 (m, 5H), 7.95-8.05 (m, 2H); 8.95 (br s, 1H)

10

Example 585

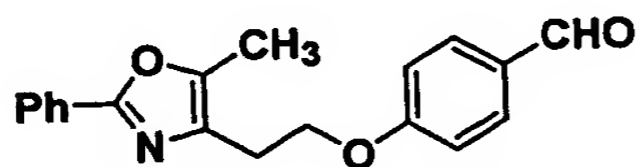
A.



15

To a -78°C solution of methyltriphenylphosphonium bromide (4.2 g; 11.8 mmol) in THF (60 mL) was added dropwise n-butyllithium (4.7 mL of a 2.5 M solution in hexane; 11.8 mmol). The solution was allowed to warm to RT and stirred at RT for 45 min. To this mixture was added dropwise a solution of the aldehyde (3.0 g; 9.8 mmol)

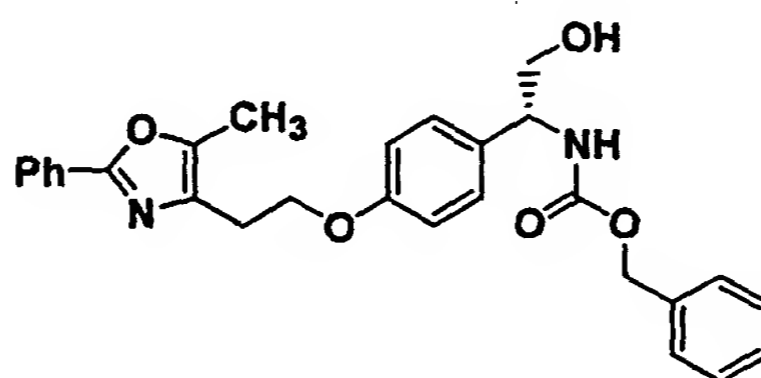
25



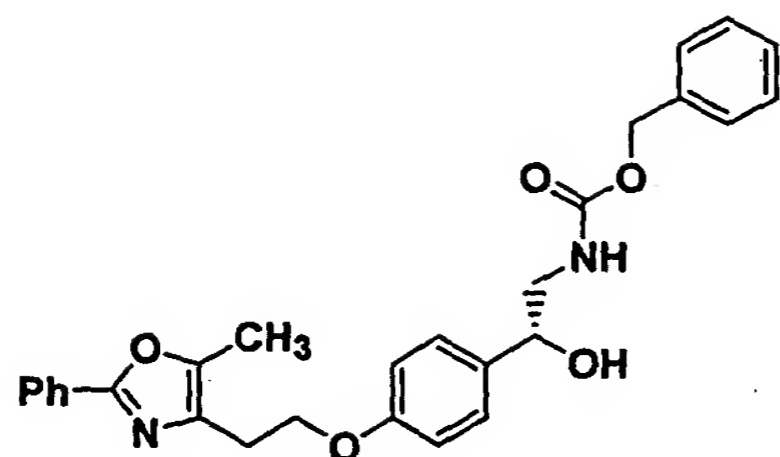
in THF (15 mL). The reaction was stirred at RT for 30 min and at 50°C for 13 h. After cooling to RT, the reaction mixture was partitioned between EtOAc and saturated aqueous NH_4Cl . The organic phase was washed with brine, dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; Hexane:EtOAc; stepwise gradient from 9:1 to 4:1) to provide Part A compound (2.0 g; 67%).

10

B.

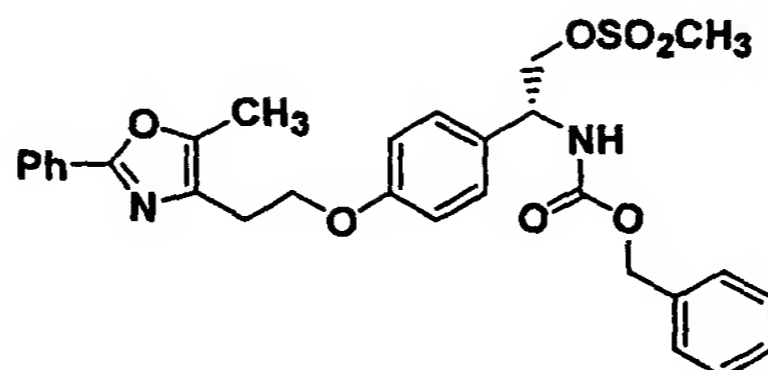


To a solution of benzyl carbamate (3.07 g; 20.3 mmol) in n-propanol (26 mL) was added a freshly prepared solution of aqueous NaOH (800 mg in 48 mL H_2O) and tert-butyl hypochlorite (2.17 g; 20.0 mmol). After stirring at RT for 5 min, a solution of hydroquinidine 1,4-phthalazinediyl diether $[(\text{DHQD})_2\text{PHAL}]$; Aldrich; 256 mg; 0.33 mmol] in n-propanol (23 mL) was added, after which the mixture became homogeneous. A solution of Part A compound (2.0 g; 6.56 mmol) in n-propanol (32 mL) was added, followed by a solution of potassium osmate dihydrate $[\text{K}_2\text{OsO}_4(\text{OH}_2)_2]$; 97 mg; 0.26 mmol] in aqueous NaOH (5 mL of a 0.4 M solution). The light green reaction solution was stirred at RT for 30 min, after which it became yellow, and was cooled to 0°C. The reaction was quenched by addition of saturated aqueous sodium sulfite (60 mL) and stirring for 15 min. The aqueous phase was extracted with EtOAc (2 x 100 mL); the combined organic extracts were washed with water and brine, dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; Hex:EtOAc; stepwise gradient from 9:1 to 1:1) to furnish Part B compound (1.80 g; 58%) and the byproduct Part C compound (0.93 g; 30%).



Part C Compound

D.

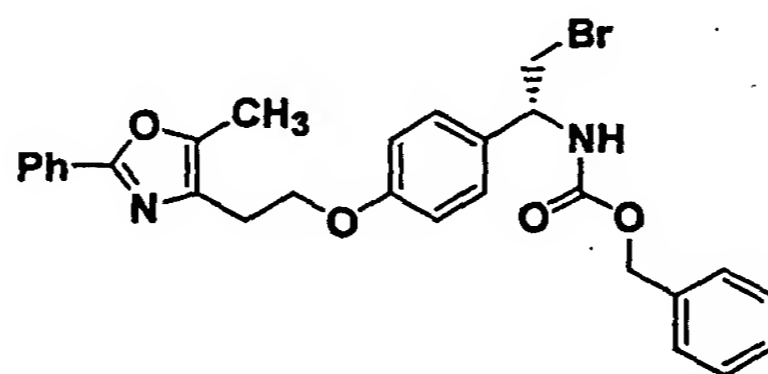


5

To a 0°C solution of Part B compound (1.10 g; 2.33 mmol) in CH₂Cl₂ (12 mL) were successively added methanesulfonyl chloride (220 µL; 2.80 mmol) and Et₃N (420 µL; 3.03 mmol) dropwise. The reaction was stirred at 0°C for 2 h, then was partitioned between CH₂Cl₂ and aqueous 1N HCl. The organic phase was washed with water and brine, dried (MgSO₄) and concentrated in vacuo to provide Part D compound (1.10 g; 86%) as a solid.

15

E.



A mixture of Part D compound (1.10 g; 2.0 mmol) and LiBr (260 mg; 3.0 mmol) in acetone (4 mL) was heated at 50°C for 14 h. The reaction was then cooled to RT and concentrated in vacuo. The residue was chromatographed (SiO₂; stepwise gradient from 9:1 to 4:1 hex:EtOAc) to give Part E compound (481 mg; 45%) as an oil.

25

CCCC[C@H](c1ccc(OCC2=C(C)O=C(NC2=O)c3ccccc3)cc1)C(=O)OCc4ccccc4

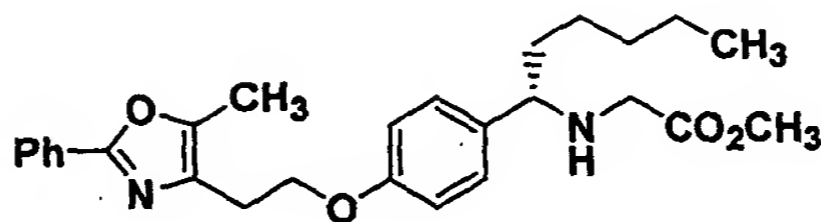
25

CCCC[C@H](N)c1ccc(OCCc2c(C)c3c(c2)nc(c3)C4=CC=CC=C4)cc1

30

and the filtrate was concentrated in vacuo to give Part G compound (18 mg; 93%) as an oil.

H.

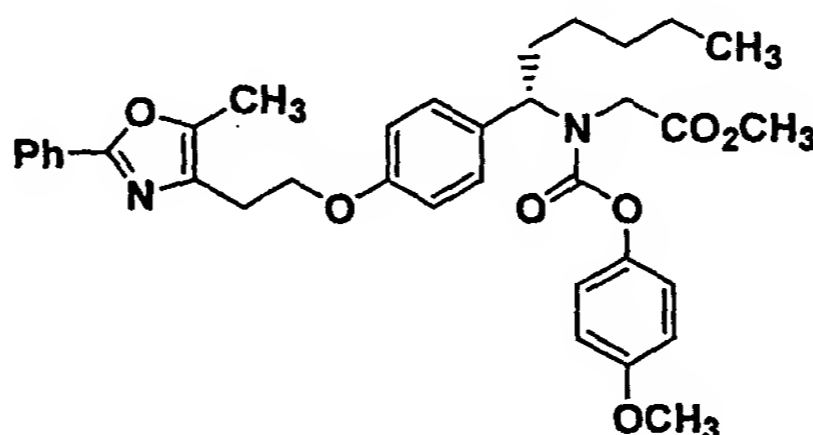


A solution of Part G compound (18 mg; 0.048 mmol), methyl bromoacetate (9 μ L; 0.095 mmol) and Et₃N (15 μ L; 0.10 mmol) in THF (500 μ L) was stirred at RT for 15h.

10 The reaction mixture was partitioned between H₂O and EtOAc (60 mL) each. The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo to furnish crude Part H compound, which was used in the next step without further purification.

15

I.



A solution of crude Part H compound, 4-methoxyphenyl chloroformate (21 μ L; 0.143 mmol) and 4-dimethyl-aminopyridine (4 mg; 0.033 mmol) in pyridine (10 mL) was heated at 70°C for 2 h. The reaction mixture was partitioned between EtOAc and 1M aqueous HCl. The organic phase was washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse phase ODS 20 x 100 mm column; 10 min continuous gradient from 50%A:50%B to 100%B + 10 min hold-time at 100% B, where Solvent A = 90:10:0.1 H₂O:MeOH:TFA, and Solvent B = 90:10:0.1 MeOH:H₂O:TFA; flow rate = 20 mL/min; retention time = 14.6

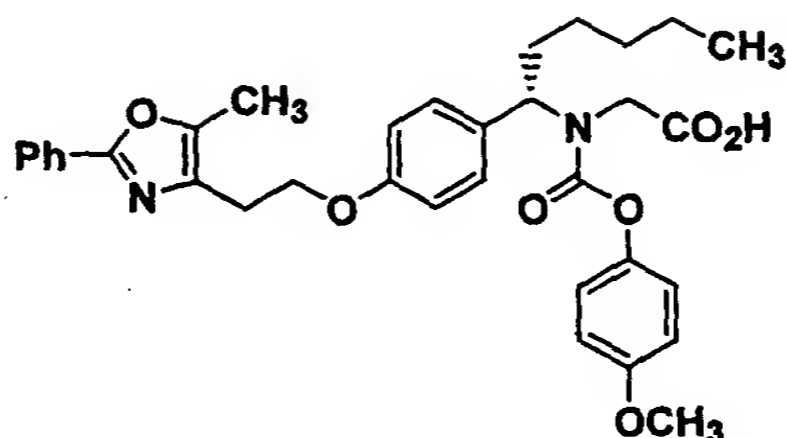
20

25

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min) to furnish Part I compound (16 mg; 56% over 2 steps) as an oil.

J.



5

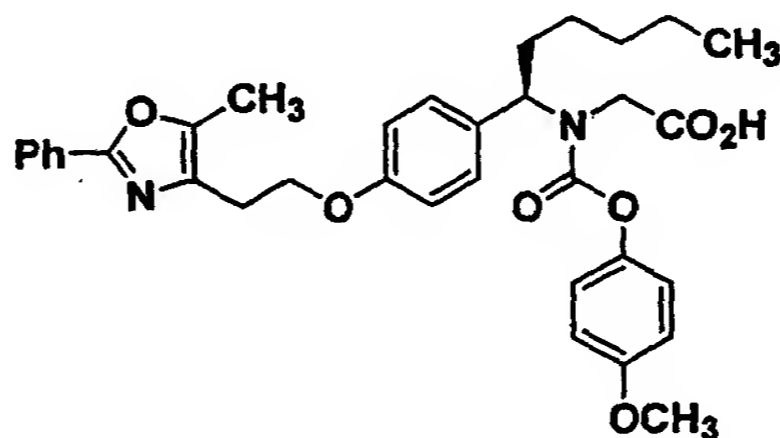
To a solution of Part I compound (9.0 mg; 0.015 mmol) in THF:H₂O (750 μ L of a 2:1 solution) was added LiOH.H₂O (2.5 mg; 0.06 mmol). The reaction was stirred at RT for 15 h; then EtOAc (2 mL) was added and the solution acidified with 1 N HCl solution to pH ~ 2. The organic phase was washed with water and brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 50:50 B:A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1 H₂O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H₂O:TFA; retention time = 13.2 min) to provide the title compound (6.0 mg; 68%) as a white solid.

20

$$[M + H]^+ = 587.3$$

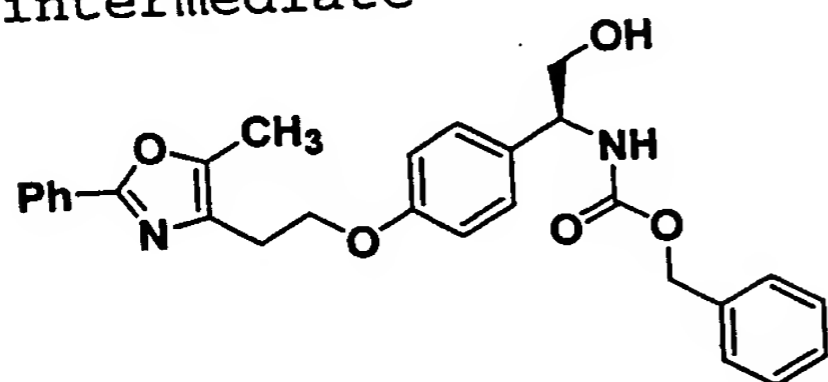
Example 586

25



The synthesis of Example 586 was performed using the identical sequence as described for Example 585 except

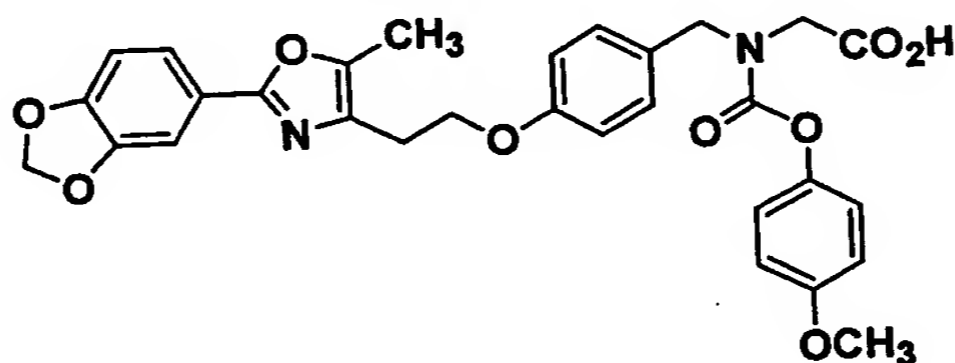
that the catalyst used in the aminohydroxylation procedure (step 2) for the preparation of the key intermediate



5 was hydroquinine 1,4-phthlazinediyl diether [(DHQ)₂PHAL; Aldrich] instead of hydroquinidine 1,4-phthlazinediyl diether [(DHQD)₂PHAL; Aldrich].

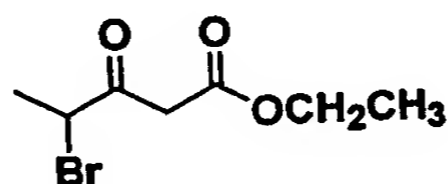
10

Example 587



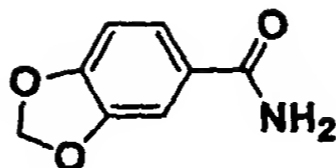
15

A.



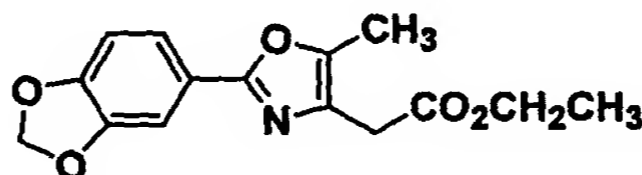
To a 0°C solution of ethyl propionylacetate (10.0 g, 69.4 mmol) in CHCl₃ (60 mL) was added dropwise a solution of Br₂ (3.6 mL; 69.4 mmol) in CHCl₃ (20 mL) and the resulting mixture was stirred at 0°C for 0.5 h. The reaction was allowed to warm to RT and stirred at RT for 0.5 h. Air was then bubbled into the mixture for 1 h. Volatiles were then removed in vacuo to yield an oily residue to provide crude Part A compound (15.3 g, >95% yield) as an oil which was used in the next reaction without further purification.

B.



To a mixture of piperonylic acid (2.0 g; 12 mmol), HOBT.H₂O (2.44 g; 18.1 mmol) and NH₄Cl (1.28 g; 23.7 mmol) in DMF (48 mL) were successively added EDCI.HCl (3.45 g; 18.1 mmol) and iPr₂NEt (2.3 mL; 48 mmol). The reaction mixture was stirred at RT overnight until the starting acid had been completely consumed (by HPLC). The mixture was partitioned between H₂O (80 mL) and EtOAc (250 mL). The aqueous phase was extracted with EtOAc (250 mL). The combined organic extracts were washed with aqueous 1 N HCl (40 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product was chromatographed (SiO₂; stepwise gradient from hex:EtOAc 1:1 to 100% EtOAc) to give Part B compound (1.5 g; 76 %) as a white solid.

C.

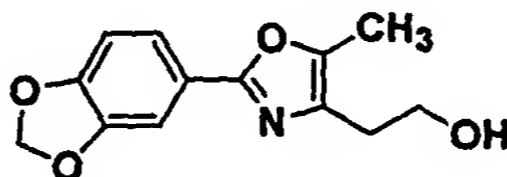


20

A mixture of Part A compound (2.11 g, 9.5 mmol) and Part B compound (1.41 g, 8.54 mmol) was heated with a heat gun until the mixture became homogeneous, after which the solution was heated at 130°C in an oil bath for 5 h. The reaction mixture was chromatographed (SiO₂; continuous gradient from hex to 4:1 Hex:EtOAc over 20 min, then continuous gradient from 4:1 Hex:EtOAc to 100% EtOAc over 15 min) to yield Part C compound (0.95 g, 39%) as a yellow solid.

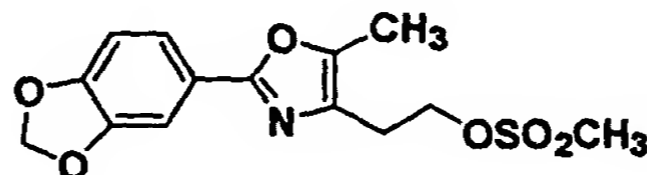
30

D.



To a -78°C solution of Part C compound (0.95 g, 3.3 mmol) in anhydrous THF (20 mL) was added LiAlH_4 (3.55 mL of a 1 M solution in THF, 3.55 mmol) dropwise over 10 min and the reaction was stirred at -78°C for 0.5 h, then at 0°C for 5 min. The reaction was quenched by sequential cautious addition of water (0.13 mL), aqueous NaOH (20 mg in 0.13 mL H_2O) and water (0.20 mL). Anhydrous MgSO_4 (400 mg) was then added to the mixture, which was stirred at RT for 10 min, then filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO_2 ; stepwise gradient from hex:EtOAc 1:1 to 100% EtOAc) to give Part D compound (350 mg; 43%) as an oil.

E.

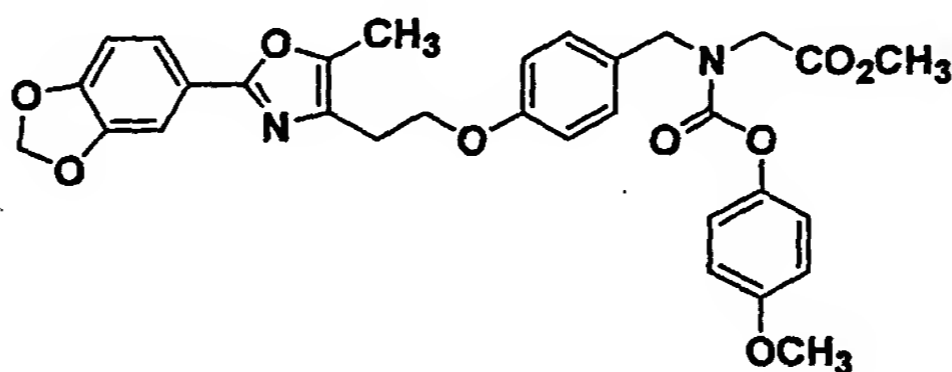


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A mixture of Part D compound (0.35 g, 1.41 mmol), $\text{CH}_3\text{SO}_2\text{Cl}$ (0.131 mL, 1.69 mmol) and Et_3N (355 μL , 2.55 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred at RT for 4 h, then partitioned between EtOAc (150 mL) and H_2O (10 mL). The organic phase was dried (MgSO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2 ; stepwise gradient from hex:EtOAc 1:1 to 100% EtOAc) to provide Part E compound (0.395 g, 86%) as a white solid.

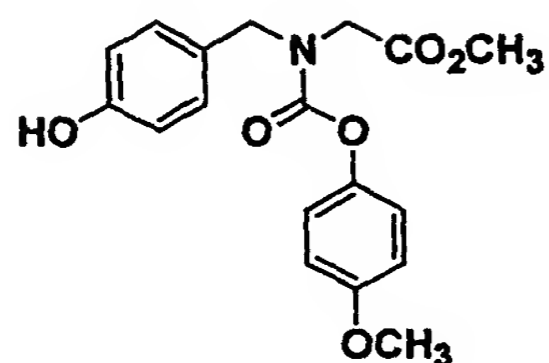
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F.



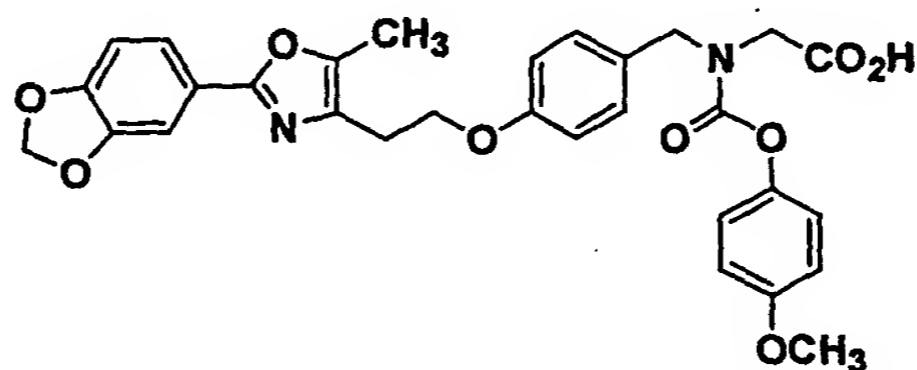
A mixture of Part E compound (25 mg; 0.076 mmol),
Example 559 Part E compound (25 mg, 0.073 mmol),

30



and K_2CO_3 (15 mg, 0.109 mmol) in acetonitrile (1 mL) was shaken and heated at $80^\circ C$ for 22 h. The reaction was cooled to RT and filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; continuous gradient over 10 min from 70:30 A:B to 100% B, where A = 90:10:0.1 H_2O :MeOH:TFA, and B = 90:10:0.1 MeOH: H_2O :TFA, with 7 min hold time at 100% B; flow rate = 20 mL/min) to provide Part F compound (21 mg; 51%) as a colorless oil.

G.



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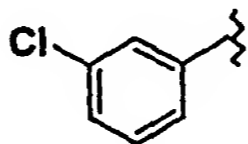
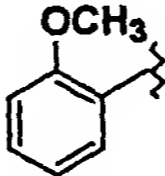
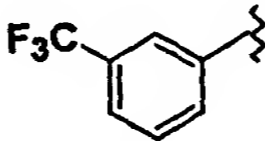
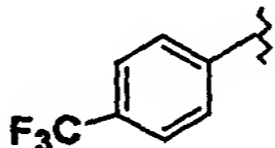
A solution of Part F compound (21 mg, 0.037 mmol) and $LiOH \cdot H_2O$ (4.0 mg; 0.095 mmol) in THF- H_2O (2.0 mL of a 1:1 mixture) was shaken at RT for 4 h. The reaction mixture was acidified to pH 5 with 1 M aqueous HCl, then was extracted with EtOAc (3 mL) by shaking for 10 min. The organic phase was washed with H_2O (2 mL) and concentrated in vacuo to provide Example 586 (16.3 mg, 75%) as a solid foam.

25

$$[M + H]^+ = 561.2$$

Examples 588 to 596 were prepared according to the scheme described above.

Cc1c(Oc2ccc(cc2)OCCN(Cc3ccc(cc3)COC(=O)O)C(=O)Oc4ccc(OC)cc4)n(c1)Ar

Example No.	Ar	[M+H] ⁺
588		551.1
589		547.2
590		585.3
591		585.2

5

Cc1oc(Ar)n1CCOc2ccc(cc2)CN(CCC(=O)O)C(=O)Oc3ccc(OC)cc3

10

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